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Editorial

Doctor Patient Relationship and Diabetes Mellitus

Introduction:

Relationship and interaction of doctors with patients and their key caregivers are assuming importance day by day.

This is of particular relevance in case of chronic illnesses like Diabetes Mellitus where long term management is necessary. American Diabetic Association and European Association for study of Diabetes have highlighted person centered care (PCC) in the management of Diabetes.

In India an explosive increase in the number of Diabetic patients has taken place over recent years. ICMR sponsored studies observed presence of 61.3 million of diabetics in India in 2000. They postulated that increased conversion from pre diabetics to diabetics and visceral adiposity might have produced such results. They further predicted that existing 77 million prediabetics may soon become full blown diabetics unless urgent appropriate interventions are taken.

Psychological Factors and PCC:

To combat this bleak scenario it is of utmost importance to implement PCC in a practical and effective way. It has to be remembered that India is a developing, multicultural and educationally as well as economically backward country. So some amount of understanding of the personality of the individual patient would help to import better patient education and guidance. The study of personality traits (as published in this issue) of diabetic patients is an important step in this regard.

Co morbidity of diabetes is known to occur with depression, anxiety disorders, obsessive compulsive disorders, obesity, substance abuse like smoking and alcohol. All these cause poor glycemic control. Among type 2 diabetes those with depressive symptoms will likely to report more stress associated with having the disease, leading to an increase in negative outlook of life, which in turn will be associated with more avoidance and passive behaviour. This is a vicious cycle since the increase in avoidance and passive behaviour leads to more depressive symptoms and greater diabetes related stress.

Moreover certain antipsychotics specially clozapine and Olanzapine may lead to obesity and subsequent metabolic syndrome and diabetes.

Study of personality traits offer new insights into variations in glycemic control in patients with type 2 diabetes undergoing standard management. Patients with type 2 diabetes differ from control group members in terms of higher levels of anxiety and depression as well as the temperament and character traits of fatiguability, resourcefulness and helpfulness.

Concluding Notes:

It may be concluded that some amount of knowledge about the psychological profile of a patient helps to understand him as an individual. Ideas of his character traits as well as his positive and negative qualities will help to frame the

strategies of PCC. Such an endeavor may not need great knowledge of psychology or psychiatry, simply sympathetic listening and efforts to understand patients practical problems will help. Thus a small effort on the part of an empathic physician may help to enhance his patients quality of life and reduce caregiver burden.

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Some Patients with Diabetes Possess Personality Traits That Enable Them to Better Control Their Disease

Smt. Mili Bandyopadhyay[1], Dr. Anirban Mazumdar[2], Dr. Sudip Chatterjee[3]

Abstract:

Control of diabetes is a lifelong process which requires intensive partnering between the patient and the care giving team. Extensive patient education has long been recognized as the cornerstone of successful diabetes management. In busy clinics in resource constrained settings such as ours, this is seldom possible due to limitations of time. We found that some patients maintained excellent control over their diabetes in spite of minimal education. These patients did not differ in age, social class or educational attainments from other less well controlled patients. However on administering Sato's simplified personality test, significant differences emerged. The well controlled patients were less extroverted and less sensitive to external cues than age matched controls.

Key Words:

Diabetes; patient behaviour; patient psychology

Introduction:

Good metabolic control in diabetes depends to a large extent on the quality and frequency of the interaction the diabetes team has with its patients. The diabetes clinic in our hospital (RKMSP) caters to patients in socioeconomic classes 4-5. All services are free and there is a nominal charge for patient registration. It is extremely busy and often there is little time for consultants to talk to patients. The patients pay subsidized charges for laboratory tests and pay standard charges for medication. In this clinic, we identified a subset of patients who were highly adherent and maintained clinical standards close to ideal at considerable cost and effort. In the absence of any special effort on our part, we wanted to know what motivated these patients to maintain excellent standards of care.

The authors were of the opinion that the diabetes education imparted to the patients in the clinic setting, was suboptimal due to constraints of time. There was no opportunity for conventional diabetes self care concepts to be taught either individually or collectively. Yet many patients achieved exemplary control. The objective of this study was to examine the behavioural traits of the well controlled patients and to identify the beneficial skills they possessed.

Material:

The study was conducted on established patients of the Diabetes OPD of RKMSP between May and November 2010. An established patient was defined as one who had visited the clinic at least 3 times prior to May 2010 and had visited the clinic at least two times during the study period. There were 1084 such patients. Of these 24 patients were felt to be ideally controlled based on American Diabetes Association criteria (1) and gave their consent for further evaluation. Twenty four age and sex matched control patients

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were randomly selected for purposes of comparison.

The Eysenck Personality Questionnaire, brief version was obtained with the help of Dr. Toru Sato, Department of Psychology, Shippensburg University, Shippensburg, PA, USA (2). This was translated into the local language (Bengali) and validated. According to Eysenck (3) the basic personality traits are extraversion, neuroticism and psychoticism. The original scale measured these three components and had a 'lie scale' and required a yes or no response. Sato's brief 24 question version had a 5 point scoring system and did not have the lie scale or the psychoticism measure and has been well validated. A high scoring subject is likely to be more extraverted and neurotic than a low scoring subject (Appendix-1). The study and the questionnaire were approved by the Institutions's Ethics Committee.

Methods:

One of the authors (MB) administered the questionnaire to the subjects. She was not aware of the status of the subjects whether they were well controlled or not. Each questionnaire took 45 minutes to administer.

Each subject's age, BP, BMI, HbA1c, Lipid Profile fasting and 2hrs post prandial glucose readings were recorded at each visit. As there were multiple visits, the highest of the values were considered for purposes of analysis. Statistical analysis was by unpaired Student's 't' test and the level of significance was fixed at = or < 0.05.

Results:

There were 24 patients in each group. Complete data were obtained in respect of age, Score, FBG, BMI. There was incomplete data for HbA1c and lipid profile. The data are summarized in Table-1.

The patients in the two groups were comparable in terms of their age and BMI. The well controlled group had significantly better values with respect to HbA1c, LDL Cholesterol, triglycerides and their EPQSV score. Well controlled patients had a mean score of 57.9 + -5.6 whereas the poorly controlled patients had a mean score of 68.5 +- 4.4 ($p > 0.001$). Sato's questionnaire (Appendix 1) has questions which alternately tested for extraversion and neuroticism.

Conclusion:

There are many questionnaires on managing diabetes from the patient's view point, for example (4, 5). All these assume that there are no time constraints on the diabetes care team. Unfortunately such time constraints are the reality in public hospitals in India. We found that well controlled patients tended to be less extraverted and less sensitive to external cues. Their excellent control was maintained in subsequent clinic visits after the completion of the study.

It was felt that there were some unique differences in behaviour among patients with diabetes. The differences could be identified in a systematic manner. However it was not feasible to teach behaviour modification to poorly controlled patients with a view to improving their metabolic control.

There have been recent publications (6,7,8) where the value of a patient education programme on diabetes control was evaluated.

In two studies, there was a positive impact of the programme. However in the study conducted on an economically disadvantaged group, there was no difference (6).

In this study, we found that some patients inherently maintain good control by virtue of their personality traits, even in the absence of an education programme.

Acknowledgement:

We would like to thank the Secretary, Ramakrishna Mission Seva Pratisthan for his help and support. We would like to thank Dr. T Sato for sending us the questionnaire.

Table 1: Showing the different parameters between the good control and poor control groups. Values are given with their Standard Deviations and the number of observations is given in parentheses. Student's 't' test has been used to calculate probability.

Parameter	Good	Poor	p-value
HbA1c (%)	5.94 ± 1.06 (21)	7.79 ± 1.47 (15)	>0.001
BMI	24.8 ± 2.5 (24)	25.5 ± 5 (24)	0.49
TG (mg/dl)	109.4 ± 51.5 (24)	168.5 ± 76.2 (19)	0.0043
FBG (mg/dl)	108.2 ± 20.8 (24)	170.6 ± 48.1 (24)	>0.001
LDLc (mg/dl)	98 ± 28.8 (24)	133.6 ± 24.4 (19)	>0.001
Age (yrs)	52.7 ± 9.1 (24)	47.9 ± 10.2 (24)	0.064
Score	57.9 ± 5.6 (24)	68.5 ± 4.4 (24)	>0.001

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Multinodular Goiter - A Clinical, Biochemical, Immunological and Cytological Study of 100 Cases

Dr. Uttio Gupta[1], Dr. D. Maji[2]

Abstract:

The aims and objectives:

To find out different etiopathogenetic mechanism in cases of Multinodular Goiter (MNG), so that definitive treatment can be planned for each patient.

Materials and Method:

Ultrasonography of thyroid was done in all goiter patients to confirm MNG and subsequently T3, T4, TSH by chemiluminescence method, Anti TPO antibody, FNAC of Thyroid, Tc99 Thyroid Scan (in those who had low TSH).

Results:

Among 100 patients of MNG,14% had toxic MNG (who had low TSH and high Tc99 uptake of thyroid), FNAC revealed colloid goiter 39%, autoimmune thyroiditis 38%, Papillary CA Thyroid 8% and Follicular CA Thyroid 1%. Prevalence of malignancy was 9% amongst MNG patients.

Earlier MNG was considered to be a benign condition; however of recent several studies malignancy found in MNG also.

Conclusion:

Hence, it can be concluded that, risk of malignancy in MNG is similar to single thyroid nodule and should be investigated to rule out malignancy as it has been seen in this study.

Introduction:

Enlargement of thyroid gland is considered clinically as goitre. Goitre can be diffuse, or single nodular or with multiple nodule the so called Multinodular Goitre (MNG). MNG has varied presentation and different etiopathogenic mechanisms. It can be autoimmune (Hashimoto's Thyroiditis), toxic or non-toxic MNG or malignancy.

However, the differentiation of these conditions cannot be made reliably on clinical examination alone. Several diagnostic tests such as thyroid hormone profile, ultrasonography of the thyroid gland, anti-thyroid antibodies and Fine Needle Aspiration Cytology (FNAC) are done for the diagnosis and appropriate management of the patient[1,2,3].

In our study, the aim was to find out the prevalence of different etiopathogenesis and presentation of MNG on the basis of clinical, biochemical, immunological, imaging and cytological analyses in patients, attending Endocrine OPD of our hospital, which would help us to decide the management plan accordingly.

Materials and Methods:

In this study,100 cases of Multinodular Goitre (MNG) were taken from our Ultrasound clinic who were refereed from the Thyroid clinic of

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Ramakrishna Mission Seva Pratisthan Hospital. From our clinic records it was found that on palpation of neck only 58% had MNG, 22% had diffuse goitre and 20% had solitary thyroid nodule. Ultrasonography of thyroid was done with high frequency transducer (7.5 to 15.0 MHz), and 100 sonographically confirmed MNG patients were included in the study. Subsequently other investigations were done.T3, T4, TSH by chemiluminescence method, Anti TPO antibody, FNAC of Thyroid and Tc99 Thyroid Scan (in those who had low TSH). FNAC were taken from at least 4 sites and the cytology results were categorized into 4 groups-Benign, Follicular, Malignant and inadequate sampling.

Hypothyroidism was defined as serum TSH more than 5.0 mU/l. Thyrotoxicosis as serum TSH less than 0.35 mU/l and Autoimmune Thyrroiditis as Anti TPO antibody titer more than 30.

The categorical variables are reported as number and percentage of patients and compared across groups using chi-square test for independence of attributes. An α level of 5% has been taken and hence any p value <0.05 has been taken as significant. SPSS software version 16 has been used for the analysis.

Results and Analysis:

In our study, 29% were in age group of 41-50 years, 25% in the 31-40 years age group. Only 4% were above 60 years old. So, most of our patients with MNG were in fourth and fifth decade and 82% patients were female and only 18% were male.

1. Clinical Goiter Type of All Multinodular Goiter Patients:

On clinical palpation 58% of goiter were multinodular, 22% diffuse and 20% found as solitary thyroid nodule. But on ultrasonography all the 100 patients had definite MNG.

Table:1

Goiter type	Frequency	Percent
Diffuse	22	22
Multinodular	58	58
Solitary Thyroid Nodule	20	20
Total	**100**	**100**

2. FNAC Feature of Multinodular Goiter:

In our study of 100 patients of MNG, on FNAC examination colloid goiter has the highest prevalence of 39%, autoimmune thyroiditis 38%, toxic MNG 14%, Papillary CA Thyroid 8% and only 1% has Follicular CA Thyroid.

Table:2

FNAC of Thyroid	Frequency	Percent
Autoimmune Thyroiditis	38	38
Colloid Goiter	39	39
Follicular CA Thyroid	1	1
Papillary CA Thyroid	8	8
Toxic Multinodular Goiter	14	14
Total	**100**	**100**

3. Features of Tc 99 Uptake Thyroid Scan:

In our study, toxic MNG patients, 31% had increased uptake, suggesting MNG with hyperthyroidism, 52% had decreased uptake, suggesting thyroiditis and 17% had patchy uptake.

Table:3

Uptake on thyroid scan	Frequency	Percent
Decreased	15	52
Increased	9	31
Patchy	5	17
Total	**29**	**100**

Discussion:

We conducted our study in 100 patients who were found to have MNG after ultrasonography of neck in patients presenting to our Thyroid clinic with goiter (diffuse, multinodular and single nodule) on clinical examination of thyroid gland by palpation.

Tan GH et al opined that prevalence of nodular thyroid disease is greater than 60% in healthy adults screened with sonography[4].

Schlumberger MJ et al has written that ultrasonography can confirm presence of thyroid nodule, when clinical findings are equivocal may reveal presence of non palpable nodules[5].

In our study, ultrasonography proven 100 MNG patients prior clinical palpation only 58% had multinodular goiter, 22% had diffuse goitre and 20% had solitary thyroid nodule (Table:1). Hence it can be concluded that, ultrasonography is the only reliable and confirmatory method for detection of MNG, even if nodule is not palpated clinically.

Earlier, MNG was considered to be a benign condition. But in several studies, malignancy is found in MNG also. In cold single nodule around 5-10% have malignancy of which Pap CA Thyroid is the commonest.

Tollin SR et al have opined that the risk of malignancy in thyroid nodules occurring within a MNG is similar in frequency with solitary thyroid nodule[6].

According to Contempre B et al the possibility of malignancy should be considered in all patients with MNG and ultrasonography guided FNAC and biopsy enhance the diagnostic efficacy[7].

Gupta M et al showed that a multitude of diagnostic tests like ultrasound, thyroid nuclear scan and FNAC are used for evaluation of thyroid nodule. FNAC is the Gold Standard and other tests should be used in conjunction with FNAC[8].

FNAC is the most accurate method for selecting patients needing thyroid surgery. Most centers utilizing FNA biopsy have achieved a 35–75% reduction in the number of patients requiring surgery, while still doubling or tripling the malignancy yield at thyroidectomy[9-11].

Hanumanthappa M.B. et al in their study concluded that, the incidence of malignancy in MNG is quite significant and it is not very low as was thought before. Due to the risk of occult malignancy, all the patients with MNG who are treated conservatively need a close follow up for malignancy[12].

In our study of 100 patients of MNG, on FNAC examination colloid goiter has the highest prevalence of 39%, autoimmune thyroiditis 38%, toxic MNG 14%, Papillary CA Thyroid 8% and only 1% had Follicular CA Thyroid (Table:2). So, prevalence of malignancy is 9% among MNG in this study.

Hence it can be concluded that, Ultrasonography is the only reliable and confirmatory method for detection of MNG and risk of malignancy in MNG is almost similar in solitary thyroid nodule and should be investigated to rule out malignancy as it has been done in this study.

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Ideal Basal Insulin

Prof. Jayanta Chakraborty

A significant proportion of patients with type 2 diabetes require insulin along the course of this disease, characterized by gradual impairment in β-cell function and loss of β-cell mass,as shown in UKPDS study 50% of beta cells are lost on diagnosis of type 2 diabetes. Most patients with type 2 diabetes will eventually require insulin therapy to achieve a goal A1C of < 7% as targeted by the American Diabetes Association (ADA) or ≤ 6.5% as set by the American Association of Clinical Endocrinologists (AACE).

Tight glycemic control was crucial to prevent the microvascular complications of type 1 diabetes as evidenced by the landmark trial Diabetic Control and Complications (DCCT). Similar inference was also drawn by U.K. Prospective Diabetes Study (UKPDS), in type 2 diabetes, which showed that a similar reduction in complications could be achieved by tightly controlling blood glucose. Intensive glycemic control has also been shown to reduce risk of Macrovascular complications eg.cardiovascular disease in patients with type 1 diabetes, interestingly enough this has not been statistically significant in patients with type 2 diabetes, in several studies.

A major challenge for internists when initiating insulin therapy is choosing when to use, where to use and what to use of the many insulins available today—rapid-acting, short-acting, intermediate-acting, long-acting, ultra long acting and premixed insulins. Insulin initiation is indicated when fasting Plasma fasting glucose levels are above 250 mg/dl, random glucose levels are above 300 mg/dl, or the HbA1c is above ≥10%. Insulin should also be considered whenever the HbA1c is persistently above 8.5%, when patients are already on one or more oral antidiabetics..To use insulin therapy most effectively, the regimen must be individualized, considering his or her lifestyle needs and physical and mental status and affordability.[1]

Once-daily basal insulin, instead of a rapid-acting insulin to be taken before meals or pre mixed twice daily, is more favourable and approachable not to speak of the cost effectiveness. Recently published studies have compared the effects of adding basal versus prandial insulin in patients with type 2 diabetes on oral agents. The Treat to Target in Type 2 Diabetes study group found that, although prandial insulin improved A1C slightly more than basal insulin in patients with type 2 diabetes on maximal doses of metformin and sulfonylurea, there were more incidences of hypoglycemia with the prandial short or rapid acting insulin… 2. Moreover in mild to moderate insulin requiring patients, a study of ours, has shown excellent control with once daily basal insulin.

One should remember that, although it is of utmost importance to achieve glycemic control and target A1c in the long term, this does not have to be done in hours or days. In fact, rapid improvement in glycemic control can actually be associated with adverse outcomes in terms of bleeding from proliferative retinopathy or

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even danger related to frequent hypoglycemia. Therefore, the dictum is, "Start low, and go slow".

Starting insulin with one or two injections of a long acting insulin as basal insulin is an accepted approach in the ADA's clinical guidelines. Available basal agents include insulin glargine, insulin detemir, NPH insulin- an intermediate-acting insulin or very recently introduced ultra long acting insulin Degludec.

Alternatives are basal bolus or biphasic premixed insulin preparations. These may offer the advantage of providing basal and postprandial coverage in one injection.

Early premixed insulin formulations combined neutral protamine hagedorn with regular human insulin in a 70/30 proportion (70% neutral protamine hagedorn, 30% regular). This is a stable combination and ensures that the regular insulin will not be affected by mixing with neutral protamine hagedorn. Although this provides the convenience of a basal-bolus regimen, it has the disadvantages of a prolonged time to peak (one to five hours). The advent of the rapid-acting analogues allowed premixed insulins to be administered more conveniently, within 15 minutes of a meal, and to more closely match their peak onset to postprandial glucose excursions. The two premixed insulin analogue formulations are: insulin lispro 75/25 (75% lispro protamine suspension, 25% lispro); and biphasic insulin aspart 70/30 (70% neutral protamine aspart, 30% aspart); important recent clinical trials, INITIATE, randomized 233 insulin-naive patients with type 2 diabetes who were on oral antidiabetic drugs to either glargine at bedtime or BIAsp 70/30 twice daily for 28 weeks. Initial mean HbA1c was 9.5% and 8.9% in the BIAsp group and the glargine group, respectively. Sixty-six percent of patients in the BIAsp group achieved the HbA1c<7% compared to 40% of those in the glargine group. HbA1c reduction was greater (-2.79%) in the BIAsp group compared to the glargine group (-2.36%), especially for subjects with baseline HbA1c 8.5%. Minor hypoglycemia was reported by 43% and 16%, , in the BIAsp group and the glargine group respectively. The researchers concluded that twice daily BIAsp 70/30 was superior to glargine in achieving target HbA1c in patients failing oral antidiabetic drugs, especially in those with baseline HbA1c>8.5%. But we should not forget the risk of more hypoglycemia with split-mix regimen in this study…12

Two accepted approaches for choosing a dose of basal insulin include starting with a fixed dose of 10 units per day or determining a weight-based dose of 0.2 units /kg of body weight, in presence of normal renal and hepatic function and BMI.

Although many diabetologists in India and abroad recommend continuing all oral agents, one should be cautious to the risk of hypoglycemia with concomitant insulin and sulfonylurea therapy. Metformin and other non-secretogogues may be continued. Patients should monitor and record fasting blood glucose levels every morning and should monitor more frequently if hypoglycemia prevails. Every 3 days, if the fasting blood glucose is not in the target range the dose of basal insulin can be increased by 2 units if glucose is relatively close to the fasting target (e.g. if fasting blood glucose is 130-180 mg/dl), or 4 units (if fasting blood glucose is > 180 mg/dl). If hypoglycemia with blood glucose < 70 mg/dl occurs, basal insulin should be decreased 4 units or more or stop temporarily according to the situation.

A common mistake with basal insulin dosing is increasing the dose too much before adding prandial insulin. This does not match the physiological needs and predisposes patients to fasting hypoglycemia. A rule of thumb is that a patient should not be advanced to more than 0.5 units/kg of body weight for basal insulin without first considering adding a rapid-acting insulin (e.g., 0.1 units/kg) with meals.

If A1C remains elevated = 7% after 2-3 months on basal insulin, or if prelunch, predinner, or bedtime blood glucose levels are clearly above the goal of 70-130 mg/dl despite a fasting glucose level at goal, prandial therapy should be initiated with rapid or short acting insulin or metformin.

When adding or adjusting prandial insulin, that patients should know the importance of frequent blood glucose monitoring. Patients on basal and bolus insulin therapy should monitor blood glucose no less than four times daily (at meals and bedtime).

It is often seen that insulin to be given before each meal, this may not be necessary for all patients. If prelunch blood glucose is consistently elevated > 130 mg/dl, add rapid-acting insulin at breakfast. If predinner blood glucose is elevated, add rapid-acting insulin at lunch. If bedtime blood glucose is elevated, add rapid-acting insulin at dinner. For each of these doses, one can often begin with 4 units and adjust by 2 units every 3 days until blood glucose is in range.

Insulins available for prandial coverage include regular insulin-short-acting or the rapid-acting insulin analogs. The rapid-acting analogs, including aspart, lispro and glulisine, allow a closer approximation of physiological insulin secretion. They are absorbed more rapidly than regular insulin, leading to a more rapid onset (5-15 minutes) and peak (about 30-90 minutes) and a shorter duration of action (3-5 hours). Their rapid onset allows them to be given just before meals and they should not be given more than 15 minutes before meals. Regular insulin is less expensive than the analogs. Its onset of action occurs in 30-60 minutes, requiring dosing 30 minutes before meals for best effect. Regular insulin peaks at 2-3 hours and has a duration of 5-8 hours.

Now coming to the individual basal insulin NPH INSULIN action starts 1-3hrs, peaks at 4-10hrs, duration 10-20hrs. This is a suspension of crystalline zinc insulin combined with the positively charged polypeptide,

Insulin detemir is a soluble, long-acting basal human insulin analog. The mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose. The action starts within 2hrs, no peak, ends within 16-24hrs.

The prolonged action of Detemir is mediated by the slow systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecules and albumin binding. Insulin detemir is distributed more slowly to peripheral target tissues since insulin detemir in the bloodstream is highly bound to albumin. Detemir is indicated for once or twice daily subcutaneous administration for patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia. Detemir is not for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe

hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration. For patients treated with detemir once-daily, the dose should be administered with the evening meal or at bedtime. For patients who require twice-daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose. For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, Detemir should be started at a dose of 0.1 to 0.2 U/kg once-daily in the evening or 10 units once-daily, and the dose adjusted to achieve glycemic targets. Insulin detemir confers a body weight advantage over glargine or NPH…10

Insulin Glargine: Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin. In euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH insulin. The median time between injection and onset of pharmacological effect was 14.5 hours for NPH insulin and 24 hours for insulin glargine.

The intended duration of activity of glargine is dependent on injection into subcutaneous tissue. It should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

The recommended starting dose of Glargine in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's need. The action of glargine starts within 2-4hrs, no peak, and ends in 24hrs. The longer duration of action (up to 24 hours) of glargine is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. In a study of Basal Insulin Therapy in Type 2 Diabetes 28-week comparison of insulin glargine and NPH insulin. To determine the safety and efficacy of the long-acting analog insulin glargine compared with NPH insulin in patients with type 2 diabetes who were previously treated with insulin alone.

The treatment groups showed similar improvements in HbA_{1c} from baseline to end point on intent-to-treat analysis. The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4%) and NPH insulin subjects (66.8%). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25% during the treatment period. Subjects in the insulin glargine group experienced less weight gain than those in the NPH group. They concluded, in patients with type 2 diabetes, once-daily bedtime insulin glargine is as effective as once or twice-daily NPH in improving and maintaining glycemic control. In addition, insulin glargine demonstrates a lower risk of nocturnal

hypoglycemia and less weight gain compared with NPH insulin.

In a head to head treat to target, randomized study of 964 patients glargine was required 43.5 units to achieve the primary endpoint of HbA1C of 7% compared to patients on insulin detemir who received insulin 98.5 units an increase of 76%....8 in a cockraine data base study, in Netherlands, Swinnen et al, concluded that "our analysis suggest that there is no clinically relevant difference in efficacy or safety between insulin Detemir and insulin Glargine for targeting hyperglycemia. However, to achieve the same glycemic control insulin detemir was often injected twice daily in a higher dose but with less weight gain, while insulin glargine was injected once daily, with fewer insulin site reactions. "….7

Insulin Degludec is a ultra-long-acting basal insulin that forms soluble multihexamers at the subcutaneous injection site. The difference between human insulin and Degludec is the deletion of residue ThrB30 and the addition of a fatty diacid moiety, hexadecandioyl, attached to LysB29, via a glutamic acid spacer. Once the phenol in the pharmaceutical formulation has dispersed after injection, the acyl side-chain causes Degludec to self-associate, forming large soluble multihexamers; creating a subcutaneous depot. The zinc ions slowly diffuse out from this complex, allowing Degludec monomers to dissociate and diffuse into the blood stream at a slow and steady rate. The slowly released Degludec monomers may provide a buffering effect against changes in absorption rate. The resultant smooth and stable pharmacokinetic profile at steady state provides a longer duration of action Insulin degludec "sultralong duration of action and low variability, produces a consistent glucose-lowering activity profile at steady state. Pharmacokinetic data have demonstrated that Degludec has a terminal half-life of approximately 25 hours, twice that of insulin glargine and a duration of action of more than 42 hours. This suggests that Degludec injection time may be varied from day to day, offering patients greater convenience and flexibility,…11. When needed, allowing increased flexibility for patients leading demanding, unpredictable lifestyles such as shift workers or frequent travelers crossing time zones. These situations may include patients for whom insulin is administered by a pharmacist or nurse, who may not be able to visit the patient at the same time every day.

Insulin degludec provides comparable glycaemic control to insulin glargine without additional adverse events and might reduce dosing frequency due to its ultra-long action profile. Basal-bolus regimens with insulins designed to closely mimic a physiologic profile allow many patients to reach glycemic targets. However, issues related to variability of action leading to unexpected hypoglycemia, and the need to adapt one's lifestyle to the action profile of a prescribed insulin, can prevent the achievement of good glycemic control in a safe manner. Degludec's duration of action exceeds 42 hours, providing full 24-hour basal insulin coverage and offering a consistent glucose-lowering effect, thus potentially allowing administration within a broader dosing window…11

Deciding which basal insulin to choose is up to the diabetologist and the patient. Glargine does not have a distinct peak, has onset of action within 2-4 hours, and a duration of action of 20-24 hours and be given every 24 hours at any

time of day convenient for the patient. The onset of detemir's action is 1-3 hours and its duration of action is 18-22 hours. Given this variability in duration, some patients may be able to use this insulin just once per day, whereas-others-will-require-twice-daily-injection.

Compared to these two basal insulins, NPH insulin has the advantage of lower cost. It is an intermediate-acting product, with onset of activity in 2-4 hours, a peak in 4-10 hours, and a duration of 10-18 hours and most patients are controlled with once daily or twice daily, though our experience favors once daily with good control. When evaluating which basal insulin is preferred, NPH and the long-acting analogue glargine were considered equivalent when used in combination with short-acting supplemental insulin for treatment of patients on continuous enteral feedings, this was the observation in critical care setting, published in JCEM….9.

And finally the latest addition Degludec with long action of 42 hrs. and half life of 25 hrs. is no doubt ideal basal insulin. But its prohibitory cost makes the NPH insulin still the ideal basal insulin for our country, pending the manufacturers curtail the price of Degludec.

(NB- This is a review of literature. Author and the publisher is not responsible for the inferences of different coments made in the legend by the researchers. Moreover this should not be used as treatment guidelines. Readers are to follow standard textbooks for the same)

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Hypertension

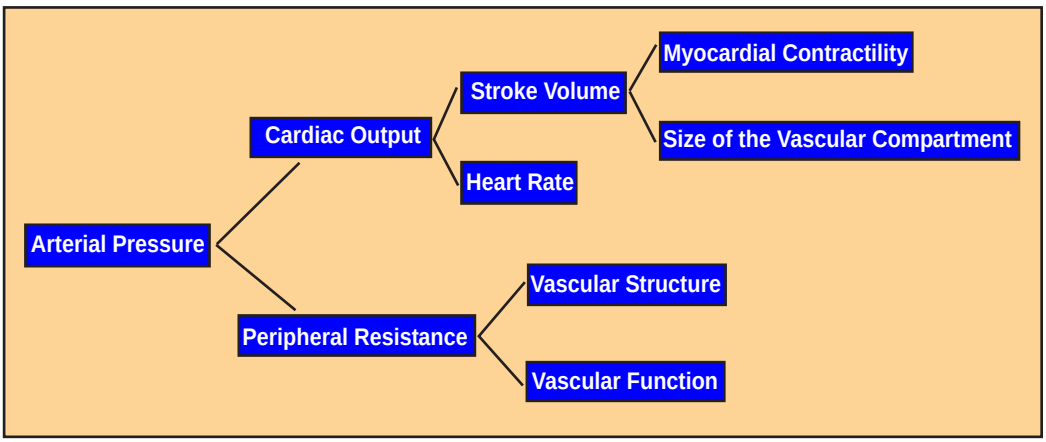
Dr. N. G. Bhattacharya[1], Dr. R. N. Chatterjee[2]

Abstract:

The pathophysiology of hypertension is an area of active research, attempting to explain causes of hypertension, which is a chronic disease characterized by elevation of blood pressure. Hypertension can be classified as either essential or secondary. Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition. About 90-95% of hypertension is essential hypertension.[1][2][3][4] Secondary hypertension indicates that the high blood pressure is a result of another underlying condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma). Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure.[5]

Most mechanisms leading to secondary hypertension are well understood. The pathophysiology of essential hypertension remains an area of active research, with many theories and different links to many risk factors.

Cardiac output and peripheral resistance are the two determinants of arterial pressure.[6] Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries and arterioles.



A Diagram Explaining Factors Affecting Arterial Pressure

Regulation of Blood Pressure:

Blood pressure is a function of cardiac output and peripheral vascular resistance two hemodynamic variables that are influenced by multiple genetic, environmental, and demographic factors. The major factors that determine blood pressure variation within and between populations include age, gender, body mass index, and diet, particularly sodium intake.

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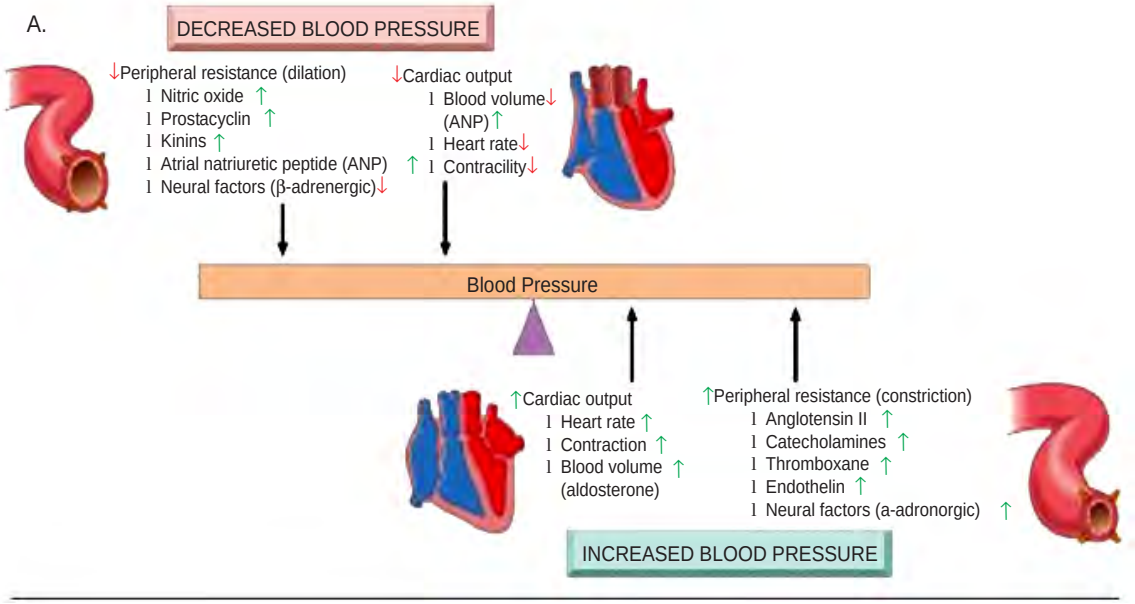
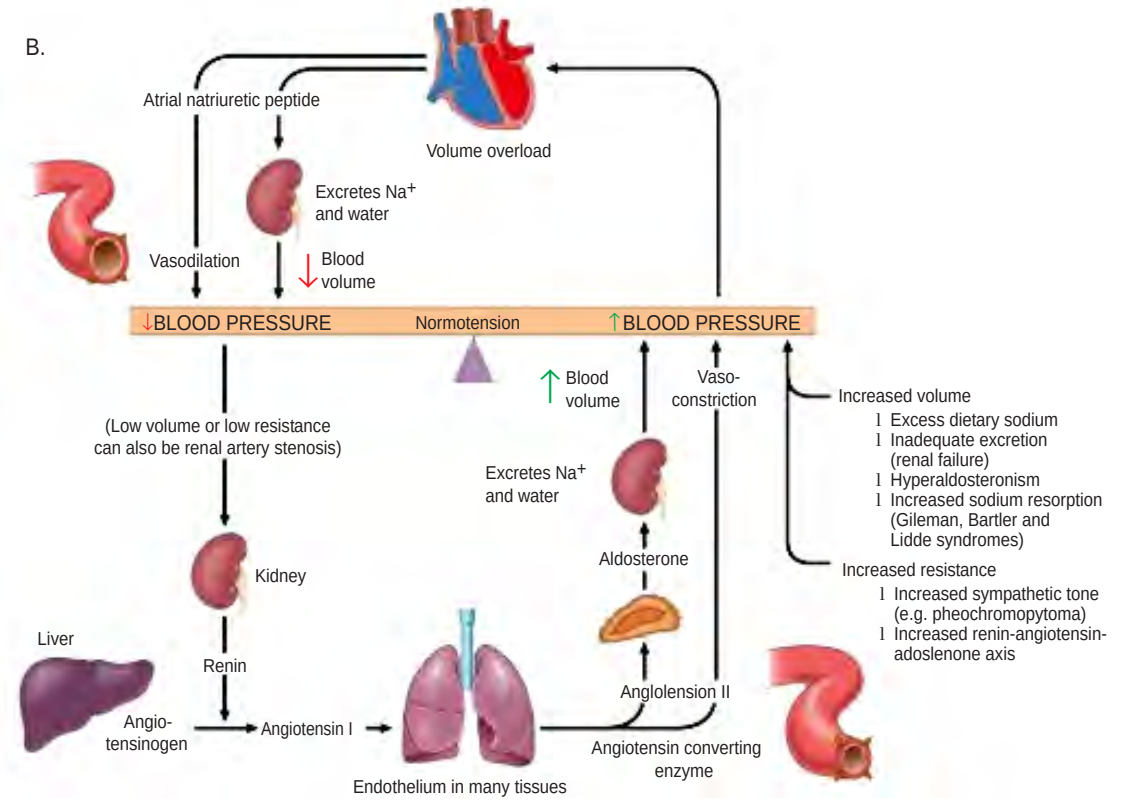

A.
DECREASED BLOOD PRESSURE
↓Peripheral resistance (dilation)
l Nitric oxide ↑
l Prostacyclin ↑
l Kinins ↑
l Atrial natriuretic peptide (ANP) ↑
l Neural factors (β-adrenergic)↓
↓Cardiac output
l Blood volume↓ (ANP)↑
l Heart rate↓
l Contracility↓
Blood Pressure
↑Cardiac output
l Heart rate ↑
l Contraction ↑
l Blood volume ↑ (aldosterone)
↑Peripheral resistance (constriction)
l Anglotensin II ↑
l Catecholamines ↑
l Thromboxane ↑
l Endothelin ↑
l Neural factors (a-adronorgic) ↑
INCREASED BLOOD PRESSURE


B.
Atrial natriuretic peptide
Volume overload
Excretes Na+ and water
Vasodilation
↓ Blood volume
↓BLOOD PRESSURE
Normotension
↑BLOOD PRESSURE
(Low volume or low resistance can also be renal artery stenosis)
↑ Blood volume
Vaso-constriction
Increased volume
l Excess dietary sodium
l Inadequate excretion (renal failure)
l Hyperaldosteronism
l Increased sodium resorption (Gileman, Bartler and Lidde syndromes)
Excretes Na+ and water
Aldosterone
Increased resistance
l Increased sympathetic tone (e.g. pheochromopytoma)
l Increased renin-angiotensin-adoslenone axis
Kidney
Liver
Renin
Angio-tensinogen
Angiotensin I
Anglolension II
Angiotensin converting enzyme
Endothelium in many tissues

Effects of Hypertension on Organs:

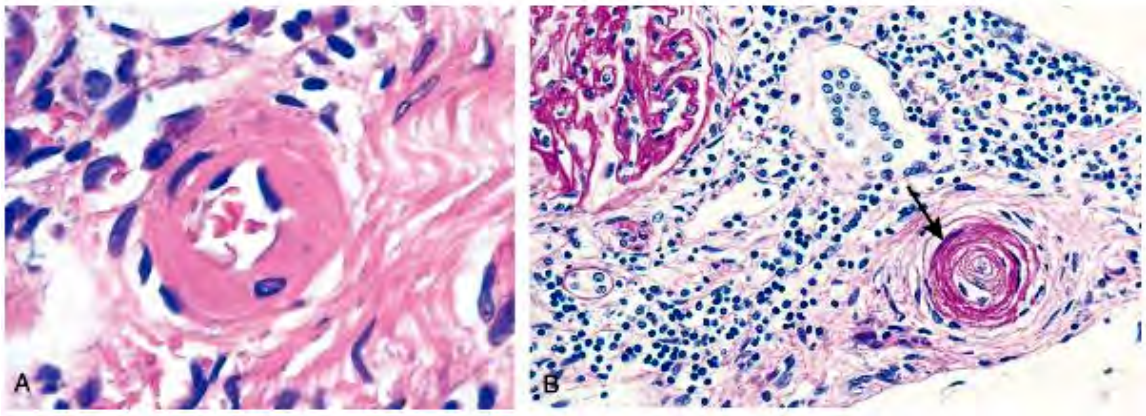
Here's a look at the complications high blood pressure (hypertension) can cause when it's not effectively controlled.

Damage to Your Arteries:

Healthy arteries are flexible, strong and elastic. Their inner lining is smooth so that blood flows freely, supplying vital organs and tissues with adequate nutrients and oxygen. If you have high blood pressure, the increased pressure of blood flowing through your arteries gradually can cause a variety of problems, including:

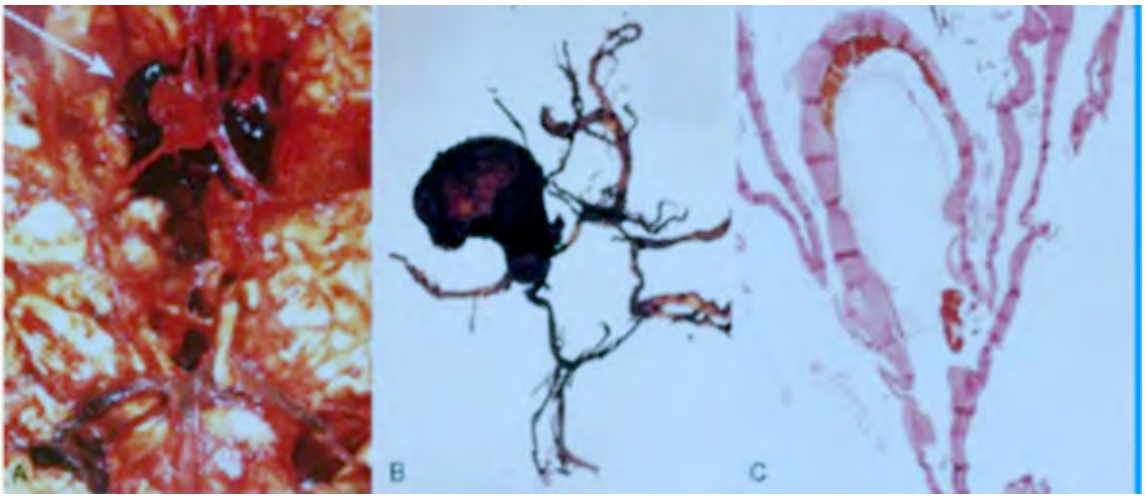
Artery Damage and Narrowing:

High blood pressure can damage the cells of your arteries' inner lining. That launches a cascade of events that make artery walls thick and stiff, a disease called arteriosclerosis (ahr-teer-e-o-skluh-RO-sis), or hardening of the arteries. Fats from your diet enter your bloodstream, pass through the damaged cells and collect to start atherosclerosis (ath-ur-o-skluh-RO-sis). These changes can affect arteries throughout your body, blocking blood flow to your heart, kidneys, brain, arms and legs. The damage can cause many problems, including chest pain (angina), heart attack, heart failure, kidney failure, stroke, blocked arteries in your legs or arms (peripheral arterial disease), eye damage, and aneurysms.



Vascular pathology in hypertention. **A**, Hyaline arteriolosclerosis. The arteriolar wall is thickened with increased protein deposition (hyalinized), and the lumen is markedly narrowed. **B**, Hyperplastic arteriolosclerosis (onion-skinning; *arrow*) causing lumenal obliteration (*arrow*; periodic acid–Schiff stain)

Aneurysm: Over time, the constant pressure of blood moving through a weakened artery can cause a section of its wall to enlarge and form a bulge (aneurysm). An aneurysm (AN-u-rizm) can potentially rupture and cause life-threatening internal bleeding. Aneurysms can form in any artery throughout your body, but they're most common in the aorta, your body's largest artery.



A, View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery *(arrow)*. **B**, Dissected circle of Willis to show large aneurysm. **C**, Section through a saccular aneurysm showing the hyalinized fibrous vessel wall (H&E).

Damage to Your Heart:

Your heart pumps blood to your entire body. Uncontrolled high blood pressure can damage your heart in a number of ways, such as:

Coronary Artery Disease:

Coronary artery disease affects the arteries that supply blood to your heart muscle. Arteries narrowed by coronary artery disease don't allow blood to flow freely through your arteries. When blood can't flow freely to your heart, you can experience chest pain, a heart attack or irregular heart rhythms (arrhythmias).

Enlarged Left Heart:

High blood pressure forces your heart to work harder than necessary in order to pump blood to the rest of your body. This causes the left ventricle to thicken or stiffen (left ventricular hypertrophy). These changes limit the ventricle's ability to pump blood to your body. This condition increases your risk of heart attack, heart failure and sudden cardiac death.

Heart Failure:

Over time, the strain on your heart caused by high blood pressure can cause your heart muscle to weaken and work less efficiently. Eventually, your overwhelmed heart simply begins to wear out and fail. Damage from heart attacks adds to this problem.

Damage to Your Brain:

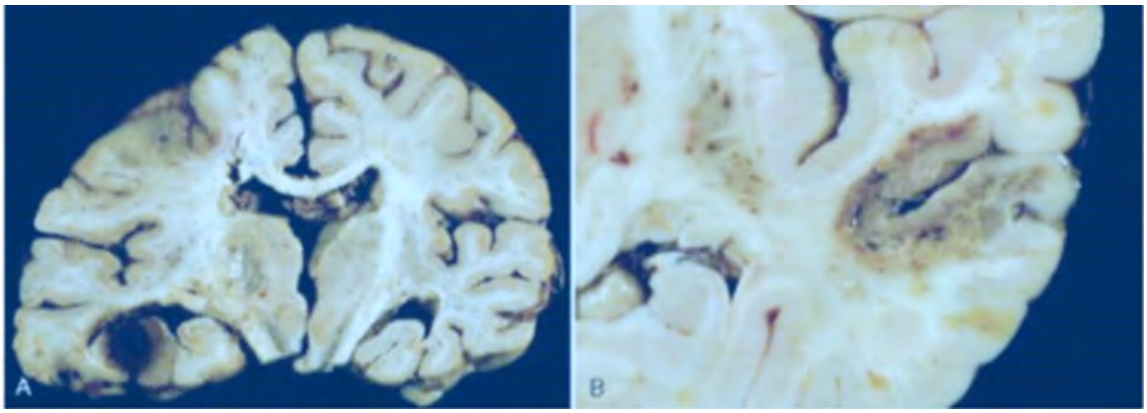
Just like your heart, your brain depends on a nourishing blood supply to work properly and survive. But high blood pressure can cause several problems, including:

Transient Ischemic Attack (TIA):

Sometimes called a ministroke, a transient ischemic (is-KEM-ik) attack is a brief, temporary disruption of blood supply to your brain. It's often caused by atherosclerosis or a blood clot — both of which can arise from high blood pressure. A transient ischemic attack is often a warning that you're at risk of a full-blown stroke.

Stroke:

A stroke occurs when part of your brain is deprived of oxygen and nutrients, causing brain cells to die. Uncontrolled high blood pressure can lead to stroke by damaging and weakening your brain's blood vessels, causing them to narrow, rupture or leak. High blood pressure can also cause blood clots to form in the arteries leading to your brain, blocking blood flow and potentially causing a stroke.



A hemorrhagic infarction is present in the inferior temporal lobe of the left side of this brain. **B**, A bland infarct with punctate hemorrhages, consistent with ischemia-reperfusion injury, is present in the temporal lobe.

Dementia:

Dementia is a brain disease resulting in problems with thinking, speaking, reasoning, memory, vision and movement. There are a number of causes of dementia. One cause, vascular dementia, can result from narrowing and blockage of the arteries that supply blood to the brain. It can also result from strokes caused by an interruption of blood flow to the brain. In either case, high blood pressure may be the culprit. High blood pressure that occurs even as early as middle age can increase the risk of dementia in later years.

Mild Cognitive Impairment:

Mild cognitive impairment is a transition stage between the changes in understanding and memory that come with aging and the more serious problems caused by Alzheimer's disease. Like dementia, it can result from blocked blood flow to the brain when high blood pressure damages arteries.

Damage to Your Kidneys:

Your kidneys filter excess fluid and waste from your blood — a process that depends on healthy blood vessels. High blood pressure can injure both the blood vessels in and leading to your kidneys, causing several types of kidney disease (nephropathy). Having diabetes in addition to high blood pressure can worsen the damage.

Kidney Failure:

High blood pressure is one of the most common causes of kidney failure. That's because it can damage both the large arteries leading to your kidneys and the tiny blood vessels (glomeruli) within the kidneys. Damage to either makes it so your kidneys can't effectively filter waste from your blood. As a result, dangerous levels of fluid and waste can accumulate. You might

ultimately require dialysis or kidney transplantation.

Kidney Scarring (Glomerulosclerosis):

Glomerulosclerosis (glo-mer-u-lo-skluh-RO-sis) is a type of kidney damage caused by scarring of the glomeruli (glo-MER-u-li). The glomeruli are tiny clusters of blood vessels within your kidneys that filter fluid and waste from your blood. Glomerulosclerosis can leave your kidneys unable to filter waste effectively, leading to kidney failure.

Kidney Artery Aneurysm:

An aneurysm is a bulge in the wall of a blood vessel. When it occurs in an artery leading to the kidney, it's known as a kidney (renal) artery aneurysm. One potential cause is atherosclerosis, which weakens and damages the artery wall. Over time, high blood pressure in a weakened artery can cause a section to enlarge and form a bulge — the aneurysm. Aneurysms can rupture and cause life-threatening internal bleeding.

Hypertenstve Retinopathy:

Hypertensive retinopathy is damage to the from high blood pressure. The retina is the layer of tissue at the back part of the eye. It changes light and images that enter the eye into nerve signals that are sent to the brain.

Causes:

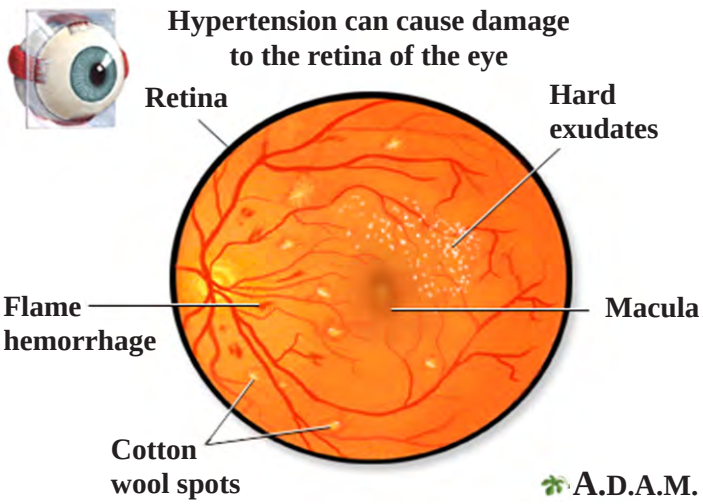
High blood pressure can damage blood vessels in the retina. The higher the blood pressure and the longer it has been high, the more severe the damage is likely to be.

When you have diabetes, high cholesterol levels, or you smoke, you have a higher risk of damage and vision loss.

Rarely, a condition called develops. Blood pressure readings suddenly become very high. Sometimes, the sudden rise in blood pressure can cause more severe changes in the eye.

Other problems with the retina are also more likely to occur, such as:

- damage to the nerves in the eye due to poor blood flow.
- blockage of the blood supply in the arteries to the retina.
- blockage of the veins that carry blood away from the retina.



Chronic Hypertension in Pregnancy

Dr. Sukanta Misra[1], Dr. Bijitbaran Chowdhury[2]

Introduction:

Hypertension is one of the commonest medical disorders affecting 10% of all pregnancies around the world.[1] Presence of hypertension affects the outcome of pregnancy adversely by influencing both maternal and perinatal morbidity and mortality. Hypertensive Disorders in Pregnancy (HDP) are classified into four categories: chronic hypertension, gestational hypertension, Pre-eclampsia and pre-eclampsia superimposed on chronic hypertension.[2] This citation would discuss chronic hypertension during pregnancy, the prevalence of which seems to be increasing as there is increasing trend of more and more women opting for childbearing at a relatively older age and many of them are overweight/obese. Population-based data indicate that approximately 1% of pregnancies are complicated by chronic hypertension. The prevalence varying according to age, race and BMI and the criteria used to establish the diagnosis.

Physiological Change in BP During Pregnancy:

Usually, there is slight drop in BP in the early pregnancy possibly mediated through the action of local mediators like prostacyclin and nitric oxide and reaching the nadir around 20 weeks of gestation. Thereafter, BP continues to rise gradually until term when pre-pregnancy levels are attained. Immediately after delivery, there is a slight drop in BP, followed by slow gradual increase over a period of few days.

Definition of Hypertension:

Hypertension is defined as SBP of = 140 mm Hg or DBP of = 90 mm Hg or both. To establish the diagnosis of hypertension, these criteria should be documented on at least two occasions, 4 to 6 hours apart. Hypertension is further classified as mild (SBP = 140-159 or DBP = 90-109 mm Hg) and severe (SBP = 160 or DBP = 110 mm Hg). For accurate measurement of BP in pregnant women, there are several general recommendations, an essential element for both diagnosing and monitoring HDP.

Definition of Chronic Hypertension:

Chronic hypertension during pregnancy is defined as hypertension present before pregnancy or before 20 weeks of gestation. Women with history of pre-pregnancy antihypertensive use and those with persistent hypertension 12 weeks after delivery are also considered as having chronic hypertension[3]. For considering management, a subgroup[4] of women having comorbid conditions (such as preexisting diabetes, renal disease and vascular disease) that represent major cardiovascular risk and impact antihypertensive therapy outside of pregnancy were identified.

Effect of Chronic Hypertension on Pregnancy:

Most women with mild essential hypertension have uncomplicated pregnancies. However, chronic hypertension is associated with several adverse pregnancy outcomes like preterm birth, IUGR, IUD, placental abruption and CS delivery.

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The risk of fetal and maternal complications increases markedly in presence of severe hypertension, prolonged hypertension, secondary hypertension, uncontrolled hypertension or superimposed pre-eclampsia.

The risk of SGA increases by almost two times and the incidence of SGA reaches 50% in presence of superimposed preeclampsia. Perinatal mortality is increased by two to four times than in the general population.

Women with uncomplicated chronic hypertension have three times the risk of CS delivery and twice the risk of PPH, compared with normotensive women. The risk of developing superimposed pre-eclampsia is approximately 25% with mild hypertension, rising to as high as 50% in those with history of pre-eclampsia in a previous pregnancy, severe hypertension or secondary hypertension and those with end-organ disease. Compared to normotensive women, there is fivefold increased risk of complications like maternal mortality, cardiac dysfunction due to ventricular hypertrophy, cerebro-vascular accidents, pulmonary edema and renal failure in women with longstanding hypertension and preexisting co-morbid conditions.

Effects of Pregnancy on Chronic Hypertension:

The physiological changes in pregnancy can affect chronic hypertension. Increased blood volume and decreased colloidal oncotic pressure may contribute to cardiac decompensation. Decrease in systemic vascular resistance may lead to fall in BP (may be misleading for the clinician) which reaches its nadir at around 16-18 weeks and then increases gradually reaching pre-pregnancy value by third trimester.

Evaluation:

Ideally the evaluation should be performed before pregnancy or at least as early in pregnancy as possible. The aim is to identify end organ damage and to look for causes of secondary hypertension. Depending on the severity of hypertension, the evaluation includes assessment of kidney, heart, eye and other organs.

Because kidney is affected early in the disease process and because proteinuria is the key diagnostic criteria of super-imposed pre-eclampsia, it is recommended that all women should have assessment of renal function which includes serum creatinine, BUN, 24 hours urinary protein excretion or spot protein / creatinine ratio and creatinine clearance. In addition, those with long standing hypertension, having risk for IHD, cardiomegaly and retinopathy, need to be evaluated by ECG, echocardiography and ophthalmological tests.

Traditionally, pre-eclampsia has been defined as hypertension plus significant proteinuria, defined as = 300 mg of protein in a 24 hour urine sample. Considering the inaccuracies of 24 hour urine collection, some guidelines[4,6] consider a spot urine protein: creatinine ratio of = 30 mg protein/mmol creatinine as significant proteinuria. Preeclampsia can also occur without proteinuria, since there is evidence that end-organ complications can occur without proteinuria[4,5]. Therefore, superimposed preeclampsia should be suspected in presence of new onset proteinuria, significant increase in baseline proteinuria, detection of abnormal laboratory values or development of symptoms of pre-eclampsia[3].

The various adverse conditions included in the consideration of pre-eclampsia are maternal end-organ dysfunction, maternal symptomatology, abnormal maternal laboratory testing and evidence of fetal morbidity[4]. Adverse conditions

that are reflective of maternal end-organ dysfunction include eclampsia, pulmonary edema, stroke, placental abruption and severe hypertension. Resistant hypertension, defined as hypertension that requires three medications for BP control after 20 weeks gestation is also included as adverse condition[4]. The symptom-based adverse conditions include symptoms that may reflect occipital cortical or other cerebral ischemia or edema (severe headache, visual disturbance), hepatic capsular irritation (epigastric or right upper quadrant pain) or pulmonary edema (dyspnea). Other maternal symptoms that raise suspicion for preeclampsia include severe nausea and vomiting and chest pain. Abnormal maternal laboratory testing reflecting end-organ dysfunction includes elevated liver enzymes and thrombocytopenia. Elevated serum creatinine and low serum albumin (< 2.0 g/dl) has been associated with an increased risk of pulmonary edema and other complications[4]. Signs of fetal morbidity like oligohydramnios, IUGR, abnormal Doppler umbilical artery velocimetry and IUFD are also included as adverse conditions[4,5]. Hyperuricemia, although associated with perinatal complications is not predictive of adverse maternal outcomes[4]. A serum uric acid level of = 5.5 has a likelihood ratio of 2.5 for superimposed preeclampsia[3].

Although majority of the women with chronic hypertension have been classified as primary or essential hypertension, in at least 10% cases, an underlying secondary cause may be present and include renal, adrenal, endocrine, collagen vascular diseases, coarctation of aorta and obesity (see box1). The laboratory tests to identify such causes should always be performed in consultation with an appropriate specialist. It is likely that many women have already been evaluated before pregnancy. Renal artery stenosis should be considered in young women (< 30 years) with severe hypertension, especially if there is no family history of hypertension[3]. Evaluation for pheochromocytoma is recommended for women with paroxysmal hypertension, frequent hypertensive crises, seizure disorders, anxiety attacks, palpitations or headaches[7].

When a woman presenting first time with a very high BP late in pregnancy, it is often difficult to differentiate severe hypertension from superimposed preeclampsia. However, most young nulliparous women who present with hypertension for the first time during late pregnancy will have preeclampsia. In addition to proteinuria other helpful tests include Hb, haematocrit, platelet count and LFT. Oliguria and raised Hb and haematocrit usually suggest haemoconcentration, indicative more of preeclampsia. Serum uric acid is more commonly elevated in preeclampsia. Serum creatinine may be raised in preeclampsia. Noninvasive impedance cardiography is being investigated for better differentiating worsening chronic hypertension from superimposed preeclampsia. Single biomarkers (soluble fms-like tyrosine kinase-1 and soluble endoglin levels), Doppler and combination of these tests have although been suggested as markers to differentiate superimposed preeclampsia from chronic hypertension, require more studies before being implemented in clinical practice. If the more common diagnosis of chronic hypertension or preeclampsia does not apply, the woman should be screened for SLE and primary renal disease[3].

Preconception/Initial Visit Counseling and Evaluation:

Preconception counseling should be provided

regarding treatment strategies, risks of medication and alternatives. Ideally before conception, RAAS drugs should be discontinued and evaluation should be done to look for evidences of end-organ damage and to identify possible causes for secondary hypertension. Counseling should also include emphasizing the benefit of appropriate health behavior to optimize pregnancy outcomes. Upon discovery of intrauterine pregnancy, ACE inhibitors and ARBs must be changed to alternative drugs and detailed evaluation must be done.

Risk Reduction for Preeclampsia:

a. Aspirin

To reduce the risk of preeclampsia and its complications, low-dose aspirin is recommended for women who are at high risk for development of preeclampsia. The high risk group includes women with chronic hypertension, HDP during a prior pregnancy, chronic kidney disease, autoimmune disorder, pre-existing diabetes. Although there is no clear evidence for a dosage cutoff, low-dose aspirin is commonly defined as 75 mg/day. NICE guidelines[6] recommend a dosage of 81 mg/day. Enteric coated aspirin should be avoided. Aspirin therapy should begin as early as possible for maximal benefit and should continue until delivery. Maximum risk reduction is expected if aspirin therapy is initiated before 16 weeks gestation[6]. WHO recommends initiation prior to 20 weeks gestation[1]. Continuing aspirin therapy until delivery does not increase bleeding complications. It is recommended that aspirin prophylaxis can be given at bedtime[4].

b. Others

WHO guidelines[1] recommend supplementation with 1.5-2 grams elemental calcium per day for women at high risk for preeclampsia in areas where dietary calcium intake is low. There is consensus across guidelines that salt restriction is not recommended solely to prevent preeclampsia. WHO guidelines[1] do not recommend rest at home for the prevention of preeclampsia in women at risk. Low to moderate intensity exercise is of benefit for general health. Poorly controlled chronic hypertension is a relative contraindication[8] to aerobic exercise in pregnancy.

Non-Pharmacological Treatment:

There is little evidence that non-pharmacological treatment is of any benefit at all. Women with chronic hypertension should be encouraged to keep their dietary sodium intake low, either by reducing or substituting sodium salt, because this can reduce blood pressure[4,6]. Whether bed rest is effective or not requires larger trials. However, the issue of DVT as a side effect of prolonged immobilization should be addressed.

Antihypertensive Therapy:

The goal of BP management is to optimize pregnancy outcome maintaining a balance between maternal and fetal/neonatal risk. As yet, there is no definitive evidence to define the optimal BP targets and the optimal management of mild hypertension.

Antihypertensive therapy for mild hypertension (140-159/90-99 mmHg) may decrease the relative risk of maternal severe hypertension, but there is no evidence of a positive impact on adverse maternal or perinatal outcomes. On the contrary, there is some evidence that such therapy may cause harm, such as an increased risk of SGA or LBW babies. There is limited, good quality evidence against treatment of mild hypertension and insufficient evidence regarding the benefit of treatment in prevention of maternal

stroke or other maternal morbidity or in the prevention of adverse neonatal outcomes. The existing evidence fails to identify the threshold for starting antihypertensive therapy for women with mild chronic hypertension. If BP is < 150/100 mmHg and there are no complicating factors[3], it is reasonable to withhold or reduce medication for those on antihypertensive therapy. Women with mild hypertension are, however, candidates for lifestyle modification[4,9].

To prevent severe hypertension, antihypertensive therapy should be reinstituted,[6,9] if SBP reaches 150-160 mmHg or DBP 100-110 mmHg. Antihypertensives should also be continued[9] for those women with target organ damage or who required multiple antihypertensive agents for control of BP before pregnancy.

There is no consensus regarding the optimal target for BP control. The target BP varies from 130-155/80-105 mm Hg[4], if there are no comorbid conditions, to < 150/100 mmHg[6]. For women with chronic hypertension and end organ damage, such as renal disease, a target BP of 130-139/80-89 mmHg is recommended[4]. Lowering DBP below 80 mm Hg is not recommended[4,6], because of the risk of compromising utero-placental perfusion.

Identification of severe hypertension (SBP = 160 or DBP = 110 mmHg or both) in the OPD requires in-patient admission and immediate management to lower BP to less than severe levels (< 160/110 mmHg), with a caution to avoid a precipitous or extreme drop in BP, to prevent maternal stroke and possibly to avoid IUGR. To avoid prolonged exposure to severe SBP and loss of maternal cerebral vascular autoregulation, the target BP of 140-160/90-100 mmHg is recommended[10] and < 150/100 mmHg but DBP not < 80 mmHg[6].

Although antihypertensive medications of all classes have been used in pregnancy, it is difficult to identify a single preferred agent for non-acute BP management. However, there is consistency across the guidelines regarding the acceptability of oral labetalol, methyldopa and nifedipine.

Labetalol is preferred due to fewer adverse effects than methyldopa, and is recommended[6,7] as a good option for first line treatment. The alternatives are methyldopa and nifedipine after consideration of maternal, fetal and neonatal side effect profiles. Methyldopa is preferred because of stable uteroplacental flow and fetal hemodynamics, as well as an absence of long term adverse effects in children. However, methyldopa has been associated with serious adverse effects, like hepatitis, hemolytic anemia, depression, drowsiness and a lupus-like syndrome. The evidence for long acting calcium channel blockers is limited, but they appear to be safe, although there is a theoretical concern[7] regarding potential synergy between magnesium and calcium channel blockers with resultant severe hypotension.

Regarding β-blockers, although acebutolol, metoprolol, pindolol and propranolol are accepted by some[4] the possible associations of IUGR with highly selective β-blockers were reported by others[5]. Atenolol has been associated with low birth weight when used from early pregnancy, and it is not recommended for use during pregnancy. A possible association of metoprolol and IUGR has also been reported, and metoprolol may also exacerbate asthma. Because diuretics can restrict normal plasma volume expansion of pregnancy, these are not used as first line agents but these are probably safe[7,9]. Therefore, thiazide diuretic used before pregnancy does not need to be discontinued

during pregnancy. The possible adverse effects of thiazide diuretics are hypokalemia and carbohydrate intolerance. Hydrochlorothiazide and Hydralazine are considered as adjunctive agents among oral antihypertensives used commonly in pregnancy[3]. A summary of standard and maximum dose ranges of common agents is noted below. (See table 1).

Severe hypertension with or without preeclampsia requires urgent treatment. Parenteral hydralazine or labetalol are most commonly used in this setting, although calcium channel blockers, ketanserin, diazoxide and others have been used[3]. A systematic review[11] of 24 RCTs concluded that although various drugs are effective, no particular agent was better than the other. A meta-analysis[12] noted that parenteral hydralazine was less effective than nifedipine in lowering BP to target range, but hydralazine was more effective than labetalol. However hydralazine has more adverse maternal and perinatal events such as maternal tachycardia and delayed maternal hypotension than labetalol. Therefore experience and familiarity of the clinician with a particular agent with its potential feto-maternal adverse effects should dictate the selection of the agent[3]. A summary of agents for urgent control of severe hypertension in pregnancy is noted below. (See table 2).

Because of the increased risk of congenital abnormality drugs that act on the renin-angiotensin-aldosterone system (RAAS) should not be used during pregnancy. In fact these drugs are contraindicated[3] in all trimesters of pregnancy. These drugs include ACE inhibitors, angiotensin receptor blockers (ARB) and direct renin inhibitors. Because = 50% of the pregnancies are unplanned, these drugs should better be avoided in women of reproductive age group. If these medications are unavoidable, then the woman should be counseled regarding the use of effective contraception and also the need for discontinuation of the drugs with the use of alternative ones before planning pregnancy. There is some evidence[6] that there may be no added risk from ACE-inhibitors during the first trimester of pregnancy, but the risk is clearly present in the second and third trimesters. This study provides some reassurance to women who become pregnant while taking ACE inhibitors. Because of the risk of stillbirth, Prazosin is also not recommended[4] during pregnancy.

Maternal Surveillance:

Definitive proteinuria testing is recommended by all the guidelines either by spot urinary protein: creatinine ratio or 24-hour urine collection[4,7]. Use of an automated reagent strip reading device or urinary protein: creatinine ratio twice weekly is recommended[6] for women with non-severe hypertension. Other than proteinuria, there is insufficient evidence to define which lab assessments are most useful in monitoring women with chronic hypertension. There is poor quality evidence regarding the predictive value of specific positive tests, although negative tests can be useful. Most guidelines recommend that women with suspected preeclampsia should be evaluated with a CBC, electrolytes, serum creatinine, and liver function tests. In addition, coagulation studies (INR and aPTT, fibrinogen), serum uric acid, glucose and urinalysis are also recommended by some[4]. Raised serum uric acid may be useful in distinguishing preeclampsia in women with chronic hypertension who first present late in pregnancy[3]. The frequency of surveillance in suspected preeclampsia cases should be dictated by changes in maternal or

fetal clinical status[4] or if there is ongoing concern[6] and these guidelines specify weekly testing for women presenting with severe hypertension.

Fetal Surveillance:

Commonly recommended tests of fetal well being are non-stress test (NST), biophysical profile (BPP) without non-stress test, ultrasound assessment of fetal growth, amniotic fluid assessment and umbilical artery Doppler velocimetry. Although DFMC has been included[4] in the list, there is no definite cutoff value and maternal perception of a relative decrease in DFMC may be more important[7]. All these tests are of low specificity and no single test is superior to others. Therefore an Individualistic plan regarding the nature and timing of fetal monitoring has been suggested[6,7]. Most of the increased morbidity associated with chronic hypertension is due to superimposed preeclampsia or IUGR. Therefore, USG at first trimester for dating and at 18-20 weeks for anomaly scan followed by USG for fetal growth at regular intervals is recommended. If IUGR is suspected twice weekly NST or BPP and the use of umbilical artery Doppler velocimetry is appropriate[3]. In absence of IUGR or preeclampsia, these additional tests do not improve the outcome and therefore is recommended in selected women. There is no consensus regarding the timing or frequency of umbilical artery Doppler velocimetry and it is of limited value after 36 weeks gestation. For most[7] pregnancies, the tests can be initiated at 32-34 weeks after due consideration to the severity of hypertension, risk of fetal death, prognosis of neonatal survival and the potential for iatrogenic prematurity from false positive results.

Delivery Timing:

No RCTs have evaluated the best time of delivery for women with chronic hypertension. Delivery at term can be expected in those with mild chronic hypertension. Preterm delivery (spontaneous or iatrogenic) is not uncommon amongst women with severe hypertension or history of adverse outcome in previous pregnancy. A consensus panel[13] recommend following delivery plan: no antihypertensive required – 38-39 weeks, hypertension controlled with medications – 37-39 weeks, hypertension difficult to control – 36-37 weeks. However, delivery should be considered at 34 weeks[3] in presence of severe hypertension with superimposed preeclampsia. Antenatal steroids should be administered according to the institutional regime.

Mode of Delivery:

Vaginal delivery is preferred and cervical ripening may be offered[4]. The increased risk of bleeding due to thrombocytopenia and coagulopathy in cases of superimposed preeclampsia can be avoided by active management of third stage of labour with oxytocin. CS delivery is reserved only for obstetric indications.

Intrapartum:

Antihypertensive therapy should be continued during labor and delivery to keep BP at = 160/110 mm Hg. In absence of any contraindication, early insertion of an epidural catheter is recommended as analgesia. If epidural is not possible patient controlled fentanyl or remifentanil analgesia is recommended[5]. NSAIDs should be used cautiously[3] or may need to be avoided altogether[4,5] if hypertension

is difficult to control, or if there is oliguria, elevated creatinine or platelets < 50 x 10^9/L.

Anesthesia Concerns:

Despite absence of any good quality evidence, it is likely that women with mild chronic hypertension may undergo epidural anaesthesia safely. GA may pose a risk due to sudden significant rise of BP during intubation or extubation and difficult or failed intubation due to laryngeal edema. For fetal or maternal conditions, GA, however, may be indicated[5] and requires early anesthesia notification, aspiration prophylaxis, and attenuation of BP.

Fluid Balance:

Women with severe hypertension or those complicated by cardiovascular or renal diseases are at increased risk of fluid overload and pulmonary edema, a major cause of maternal mortality in this population. So they require special attention to fluid load and urine output[3] and any suspected fluid overload should be treated urgently in collaboration with an intensivist. There is insufficient data regarding the benefits and potential harms of central invasive haemodynamic monitoring[6,7]. Intrapartum oliguria is common, especially with oxytocin usage and if Intrapartum urine output is < 30 cc/hr for 2 consecutive hours, up to three boluses of 500 cc of crystalloid is recommend[14]. Accurate determination of volume status may be required in cases of persistent oliguria. The management of postpartum oliguria varies across the guidelines. Postpartum oliguria is usually due to hypovolemia and initial volume replacement with 500 cc of crystalloid over 20 minutes is recommended[14], with consideration of packed RBC if oliguria persists and the woman is anemic. In absence of pre-existing renal disease or rising creatinine, oliguria (15 ml/hr) should be tolerated[4] for at least the first six hours post partum.

Postpartum Surveillance:

As BP is often unstable for 1-2 weeks after delivery, close monitoring of BP during postpartum period is essential. Peak postpartum BP occurs between 3 -5 days after birth. BP should be monitored at least every 4 hours postpartum, and women should not be discharged until BP has been well controlled for at least 24 hours. Postpartum surveillance also includes confirmation of the resolution of end-organ dysfunction.

Postpartum Antihypertensive Therapy:

There is no reliable data to guide whether or not to continue antenatal antihypertensive therapy and which agent is preferred. WHO guidelines[1] recommend antihypertensive treatment in women treated with antihypertensives during pregnancy and in those who develop severe hypertension after delivery. The general consensus is that severe hypertension should be treated keeping a target BP of < 140/90 mmHg[6]. The evidence for treating non-severe postpartum hypertension is insufficient. However, in presence of comorbid conditions, they need to be treated, with a target BP of < 130 /80 mm Hg[4].

Although all antihypertensive agents are excreted in breast milk, these are usually acceptable[4]. Labetalol and propranolol are preferred if beta blockers are indicated. Diuretics can decrease lactation, and should be avoided in breastfeeding women. To avoid the risk of depression, Methyldopa needs to be discontinued within 2 days after birth with resumption of pre-pregnancy antihypertensive drugs[6]. Regarding ACE/ARB therapy, the evidences are either against[9] the use or felt to be insufficient to recommend[6].

Follow up:

Women who required antihypertensives should be reviewed[4] 2 weeks after delivery for long term management of hypertension. Follow up by a specialist requires[4] the need for antihypertensives and the requisite investigations. They should have annual BP checks and cardiovascular risk assessment, including lipids and glucose, at least every five years[5].

Risk Communication:

Women should be informed of the future risks like risk of future preeclampsia, and risk of future hypertension and its complications. The chance of recurrence of hypertension in subsequent pregnancies is 20-50%. She should also be counseled regarding family planning and offered an effective birth control method prior to discharge from the hospital. She should be informed that intervals between pregnancies of < 2 years or > 10 years including weight gain between pregnancies are both associated with an increased risk for preeclampsia and adverse outcomes. Overweight women should be encouraged[4] to attain healthy BMI and to follow appropriate health behaviors[3].

Take Home Message:

- Ideally a woman with chronic hypertension should be evaluated before pregnancy or at least as early in pregnancy as possible with an aim to identify the cause or any evidence of end organ damage.
- Women belonging to reproductive age group should avoid using ACE-inhibitors and ARBs, if possible; if not, then should use effective reversible contraception.
- ACE-inhibitors and ARBs are contraindicated in all trimesters of pregnancy.
- Women with severe hypertension require antihypertensive medications.
- Labetalol is a good option for first line treatment.
- Atenolol is not currently recommended for the treatment of chronic hypertension in pregnancy.
- In pregnant women with uncomplicated chronic hypertension the aim is to keep BP < 150/100 mm Hg.
- In presence of end-organ damage secondary to chronic hypertension, the aim is to keep BP < 140/90 mm Hg.
- Treatment should not lower DBP below 80 mm Hg.
- Pregnant women with secondary chronic hypertension should be referred to a specialist.
- Women with chronic hypertension should receive antihypertensive treatment dependent on pre-existing treatment, side-effect profiles, and teratogenicity.
- Fetal growth should be evaluated by USG.
- Timing for delivery should be decided by the gestational age, severity of hypertension, whether controlled or not, evidence of end organ damage, superimposed preeclampsia, other maternal and fetal adverse effects.
- Mode of delivery should be decided by the obstetric factors.
- After delivery, BP should be checked regularly and periodically. Antihypertensives may need to be initiated to keep BP < 140/90 mm Hg.
- Review long term antihypertensives 2 weeks after birth.

Secondary Causes of Chronic Hypertension

- **Renal Causes:**
  - Chronic glomerulonephritis,
  - Interstitial nephritis,
  - Diabetic nephropathy,
  - Polycystic kidney disease,
  - Nephropathy due to other causes
  - Renal artery stenosis
- **Adrenal Causes:**
  - Pheochromocytoma
  - Primary aldosteronism
  - Cushing's syndrome
- **Endocrine Causes:**
  - Hyperthyroidism and thyrotoxicosis
  - Diabtes Mellitus
- **Collagen Vascular Diseases:**
  - SLE
  - Systemic sclerosis
  - Periarteritis nodosa
- **Coarctation of Aorta**
- **Obesity**

Evaluation for Secondary Causes of Chronic Hypertension

- **Pheochromocytoma:**
  - Plasma metanephrines
  - 24 hour urinary unconjugated catecholamines, VMA
  - MRI or CT scan of adrenal gland
- **Primary Aldosteronism:**
  - Serum Potassium
  - Plasma rennin activity
  - 24 hour urinary aldosterone excretion
- **Renal Artery Stenosis:**
  - Renal USG
  - Doppler flow study of the renal vessels
  - MRI angiography of renal vessels

Table 1

Commonly used antihypertensives for non-acute management of chronic hypertension

Agent	Dosage /Range	Caution? Comment
Labetalol	200 – 800 mg/day, orally, BD/TD Max: 2400 mg/day	Avoid in women with asthma, systolic heart failure and cardiac conduction abnormalities
Nifedipine (extended release)	30-60 mg/day, orally Max: 120 mg/day Short acting nifedipine is not recommended due to the risk of hypotension	Correct form should be used Concern for severe hypotension if used concurrently with IV Mg.
Methyl Dopa	250-1000 mg/day, orally, BD/TD Max: 3000 mg/day	Drowsiness depression, hepatitis, hemolytic anaemia

Table 2

Antihypertensives for urgent control of severe acute hypertension in pregnancy

Agent	Dosage /Range	Caution? Comment
Hydralazine	5 mg IV/IM; then 5-10 mg every 20-40 minutes or constant infusion of 0.5-10 mg/hr	Long experience of safety and efficacy Risk of delayed maternal hypotension, fetal bradycardia
Labetalol	20 mg IV, then 20-80 mg every 5-15 minutes up to a maximum of 300 mg; or constant infusion of 1-2 mg/min	Possible less risk of tachycardia and arrhythmia than with other vasodilators Increasingly preferred as first line agent
Nifedipine	10-30 mg orally; repeat in 45 minutes if needed	Possible interference with labor

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Acute Acalculous Cholecystitis: A Review of Current Trends in Management

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Introduction:

Acute acalculous cholecystitis (AAC) may develop without gallstones in critically ill patients, and appears to be increasing in incidence[1]. Duncan first recognized it in 1844 when a fatal case of acalculous cholecystitis complicating an incarcerated hernia was reported. It is an acute necroinflammatory disease of the gallbladder with a multifactorial pathogenesis. It accounts for approximately 5-10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates. The mortality rate remains about 30% because the diagnosis remains challenging, the affected patients are critically ill, and the disease itself can progress rapidly due to a high incidence of gangrene (> 50%) and perforation (> 10%)[2].

The proportion of cases occurring in outpatients is not well-established. In our experience, approximately 10% of the patients attending OPD with acute cholecystitis are acalculous. This rise in incidence in outpatients may be due to the increasing use of ultrasound to rule out gallstones in every patient suspected of gallbladder disease. It is also possible that a few of these cases are mislabeled as acalculous due to presence of unappreciated gallstones or microcrystals.

Etiopathogenesis:

The critical factor in the pathogenesis of AAC is gallbladder ischemia/reperfusion injury. This is usually followed by bacterial invasion of ischemic tissue, like Escherichia coli, Enterococcus faecalis, Klebsiella, Pseudomonas, Proteus species, and Bacteroides. This increases mucosal superoxide dismutase and phospholipase A2 activity along with mucosal lipid peroxide content causing a significant host immune response, including activation of the coagulation cascade and platelet-activating factor[3]. There is enough evidence to support these observations along with the pathologic observation of high rates of gallbladder necrosis and perforation[4,5,6]. When performed on the gallbladder specimen, microangiography has revealed significant differences between acute calculous and AAC[7]. On one side gallstone-related disease is associated with arterial dilatation and venous filling, while AAC is associated with multiple arterial occlusions and minimal-to-absent venous filling.

The second most important factor is concentration and stasis of bile, which can inspissate in the absence of gallbladder emptying. Causes of bile stasis may include volume depletion or dehydration, use of opioid analgesics (spasm of the sphincter of Oddi), long-term therapy with total parenteral nutrition (30%) and prolonged positive-pressure ventilation with high PEEP[8,9]. Bile stasis increases the lysophosphatidyl choline concentration in bile, promoting local injury of the mucosa of the gallbladder by disrupting normal water transport. Increase in beta-glucuronidase in bile has also been implicated in causing further injury to the

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gallbladder[10]. Serial gallbladder ultrasound studies in patients on long-term TPN show that the incidence of gallbladder sludge increases from 6% during the first week of TPN to 50% at 4 weeks and nearly 100% at 6 weeks[11]. Critically ill patients are more predisposed because of increased bile viscosity due to fever and dehydration and because of prolonged absence of oral feeding resulting in a decrease or absence of cholecystokinin-induced gallbladder contraction. Interestingly, stimulation of gallbladder contraction with cholecystokinin does not prevent AAC in critically ill patients[12].

Acute calculus cholecystitis may be a complication of any major surgery, blunt trauma or major burns. The incidence of AAC following abdominal aortic reconstruction is 0.5 to 0.9%, with a slight predilection for ruptured aneurysm cases, especially in males[13].

AAC is also associated with diabetes, abdominal vasculitis, congestive heart failure, multiple blood transfusions, cholesterol embolization, and resuscitation from shock or cardiac arrest (4). Acalculouscholecystitis may also develop from secondary infection of the gallbladder, including *Candida* infections, *Salmonella* infections (typhoid), cholera, leptospirosis and tuberculosis (4). Acalculouscholecystitis can also be observed in patients with human immunodeficiency virus (HIV) infection, although it is a late manifestation of this disease[14].

Clinical Features:

Patients may present with fever and right upper quadrant tenderness. Patients with sepsis without any obvious source must also be considered for this diagnosis. Complications include gangrene and perforation, which may rarely lead to bleeding or bile embolism[15, 16]. The gallbladder is usually distended and may be palpable. Jaundice occurs in about 20% of the cases. Most of the patients are male with a mean age of diagnosis of 47 years. However, children may also be affected, especially after a viral illness or during typhoid fever.

Diagnosis:

The diagnosis is challenging, especially in the setting of a critically ill patient. The differential diagnosis of jaundice in the critically ill patient is complex, and includes intrahepatic cholestasis from sepsis or drug toxicity and “fatty liver” induced by TPN, in addition to AAC. Rapid and accurate diagnosis is essential, as ischemia can progress rapidly to gangrene and perforation. The diagnosis should be considered in every critically ill patient with a clinical picture of sepsis and no other obvious source. Physical examination and laboratory studies are very unreliable in this regard[17]. Bile culture results are negative in nearly 50% of patients with AAC, probably because of concurrent antibiotic therapy in these patients. Liver function tests may be deranged.

Ultrasound:

Transcutaneous ultrasound of the gallbladder is the most common and accurate modality to diagnose AAC in the critically ill patient. The most reliable criterion is thickening of the gallbladder wall. Deitch[18] reported 90% specificity using 3.0 mm and 98.5% specificity using 3.5 mm wall thickness cutoff, whereas sensitivity was 100% at 3.0 mm but only 80% at 3.5 mm. Based on the above findings, Deitch and Engel recommended acceptance of gallbladder wall thickness of 3.5 mm or greater as definitive evidence of acute cholecystitis, whereas 3.0 mm is suggestive but not

conclusive[19]. False-positives may occur due to presence of sludge, cholesterolosis, hypoalbuminemia, nonshadowing stones or ascites[19]. Other features for AAC are the presence of pericholecystic fluid, intramural gas (emphysematous cholecystits) or a sonolucent intramural layer or "halo" that represents intramural edema.

Cholescintigraphy:

Hepatobiliary imaging has limited value in critically ill or injured patients[20] because of a high incidence of false-positive scans, which may be due to fasting, liver disease, or TPN. A sensitivity rate as low as 68% has been reported in studies of hepatobiliary imaging for AAC. Intravenous morphine (0.01 mg/kg) may increase the accuracy of cholescintigraphy in critically ill patients. Non-visualisation of the gallbladder despite good hepatic uptake and the entry of isotope into the small intestine is taken as positive evidence of cholecystitis. Moreover, increased pericholecystic activity (the 'rim' sign) can indicate the complication of gangrene, and exceptionally free peritoneal spill will diagnose perforation of the gall bladder[21, 22]. However, cholescintigraphy is an excellent choice of investigation with high sensitivity in the outpatient setting. Gall bladder ejection fraction (GBEF) is measured, and a cutoff value of 40% (35% according to some studies) or less is considered for this diagnosis to be made. Most studies have concluded that the latent period and the pattern of gallbladder emptying as well as the onset of gallbladder filling and biliary-to-bowel transit time are of no significant diagnostic value in the diagnosis of acalculouscholecystitis.

Computed Tomography:

Computed tomography (CT) is as accurate as ultrasound in the diagnosis of AAC in critically ill patients[23]. A single retrospective study has compared all three modalities (ultrasonography, hepatobiliary scanning, and CT)[24]; ultrasonography and CT were comparably accurate and superior to hepatobiliary imaging in acute acalculouscholecyctitis. CT scan may be preferred over ultrasound if other abdominal pathology is more likely.

Laparoscopy:

Although reports are limited to small series and there has been no randomized trial, laparoscopy has been reported to be successful for both the diagnosis and therapy of AAC[25]. For critically ill patients, laparoscopy can be performed under local anesthesia and intravenous sedation. Laparoscopy is possible in patients who have undergone recent abdominal surgery if "gasless" techniques are used. Diagnostic accuracy is high, and both laparoscopic cholecystostomy and cholecystectomy have been performed.

Treatment:

The main treatment for AAC is cholecystectomy. Drainage of pericholecystic fluid collections may be done, and other acute problems that may mimic acute cholecystitis (e.g., perforated ulcer, cholangitis, pancreatitis) must be ruled out. Cholecystostomy can be a life saving alternative in the patient considered too unstable to undergo general anesthesia[26]. Successful cholecystostomy is followed by cholangiography after the patient has recovered. If gallstones are absent (true AAC), cholecystectomy is usually not indicated and the catheter can be removed[27]. However, definite statistical data is lacking whether or not interval cholecystectomy is of any role after percutaneous cholecystostomy in the treatment of AAC. One possible solution could be to perform a cholescintigraphy to assess the GBEF

after an interval of 6 weeks and perform cholecystectomy if the GBEF is less than 40%. Most studies are of the opinion that once recovered from AAC while critically ill, the gallbladder function improves and interval cholecystectomy is usually not required. Percutaneous cholecystostomy is gaining acceptance of late as an alternative to open procedures. Although randomized trials have not been published, class II and III of evidence lends credence to the procedure. The advantages of percutaneous cholecystostomy are bedside applicability, local anesthesia, and avoidance of an open procedure. In 85% cases, the patient has been noted to improve. If there is no improvement within 24 hours, an open procedure should be performed. Causes of failure include gangrene, catheter dislodgment, bile leakage and wrong diagnosis. In the largest reported series, major complications were reported in 8.7% cases, including dislodgment of the catheter, acute respiratory distress, bile peritonitis, hemorrhage, cardiac arrhythmia, and hypotension due to procedure-related bacteremia. Minor complications occurred in an additional 3.9% cases[28]. Catheters are usually removed after approximately 3 weeks in critically ill patients with AAC who have undergone percutaneous cholecystostomy. This allows for the development of a mature track from the skin to the gallbladder.

Antibiotic therapy is an important adjunct to the removal or drainage of AAC. The most common bacteria isolated from bile in acute cholecystitis are *E. coli*, *Klebsiella* and *Enterococcus faecalis*, thus antibiotic therapy is directed against these organisms. *Pseudomonas*, staphylococci (MRSA/VRSA), *Enterobacter* species, anaerobic organisms (*Clostridium, Bacteroides*), and fungi may be found.

In patients with AAC who are high-risk surgical candidates (i.e. end-stage liver disease), endoscopic gallbladder stent placement has been reported as an effective palliative treatment. This involves placement of a double pigtail stent between the gallbladder and the duodenum during ERCP.

Summary:

Acalculous cholecystitis is an acute necro-inflammatory disease of the gallbladder with a multifactorial pathogenesis. It accounts for approximately 10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates. Acalculous-cholecystitis is typically seen in patients who are hospitalized and critically ill, though it may also be seen in the outpatient setting. Ultrasonography is typically the first test obtained when acalculouscholecystitis is suspected. Advantages of ultrasonography are that it is noninvasive, can be done at the bedside, and has good sensitivity and specificity for diagnosing acalculouscholecystitis. The role of cholescintigraphy is unclear in the critically ill patient, but it has a high sensitivity in the outpatient setting. Once the diagnosis is established, prompt treatment is imperative because without it, gallbladder gangrene may develop and can result in gallbladder perforation. Treatment is by cholecystectomy or percutaneous cholecystostomy, if general anesthesia is not feasible. Patients with acalculouscholecystitis who fail to improve or worsen following cholecystostomy require cholecystectomy. There is no documented role of interval cholecystectomy for patients who have recovered from AAC.

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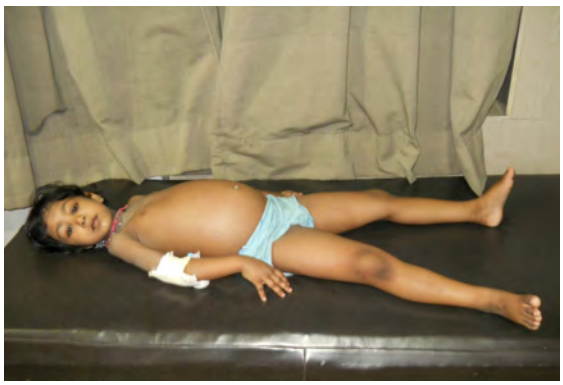
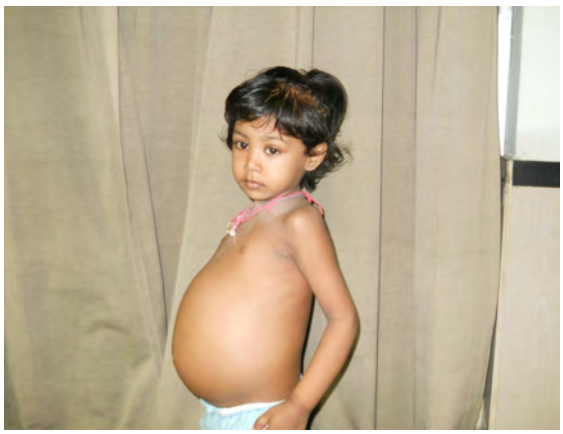
Rare Case of Pallor with Abdominal Distention: Case Report

Dr. Manomit Haldar[1]; Prof. Asha Mukherjee[2]; Dr. Akhilesh Verma[3]; Dr. Soumitra Masani[4]





Introduction:

Extra-nodal lymphoma in the gastrointestinal tract occurs in 10-30% of all patients with NHL[1]. The stomach, small bowel, pharynx, large bowel and esophagus is affected in decreasing order of frequency[2].

The cecum and the rectum are the most commonly involved part of the large bowel. The pattern of the large bowel involvement include bulky polypoidal mass, infiltrative tumor and aneurysmal dilatation[7]. Bowel obstruction is uncommon at presentation despite significant lymphomatous infiltration of the bowel wall because of the absent desmoplastic reaction[9]. In contrast to gastrointestinal adenocarcinoma, lymphoma is more likely to involve multiple and longer segments of gut and is less likely to cause bowel obstruction. Our patient presented with diffuse colonic wall thickening, 3 most common causes of which are Diverticulitis, Carcinoma and Inflammatory bowel disease. Lymphoma presenting with such an extensive and diffuse thickening of whole large gut is a rarest presentation.

Case History:

5yrs. 5 months old girl admitted on 26.06.2013 with complains of progressive distention of abdomen for last 1 month. She was also having alteration of bowel motion with passage of occational blackish stool. For the last week mother also noticed decreased urine output and periorbital and pedal edema. There was no history of vomiting, hematemesis or passage of fresh blood. On examination there was severe pallor, hugely distended abdomen (abdominal girth 61cm), no hepatosplenomegaly, no ascites.

Investigations:

On 14.06.2013 (before admission at RKMSP) Hb-5gm/dL; PCV-16.50%; MCV-54.7fL; MCH-16.9pg; TLC-10, 600/cmm ($N^{50}L^{45}M^{2}E^{3}B^{0}$); Platelet count-5.32 lakhs/cmm; ESR-35 mm in 1st hour, Peripheral smear not suggestive; Retic count-3.5%.

[1, 2, 3, 4] V.I.M.S., RKMSP

DCT-Neg; On HPLC no abnormal Hb band seen; Serum Bilirubin-0.5mg/dl (conjugated 0.2 and unconjugated 0.3); Serum urea 25mg/dL, creatinine 0.5mg/Dl; total protein 3.9gm/dL (Alb2.2 and Glb 1.7); SGPT-32U/L; Alkaline Phosphatase-170U/L; GOT-28U/L. Serum iron 26mcg/dl; Ferritin 13.5ng/ml; TIBC-252 mcg/dl; Urine and stool RE was normal. USG of whole abdomen revealed a mild hepatomegaly, multiple dilated bowel loops with small amount of free fluid.

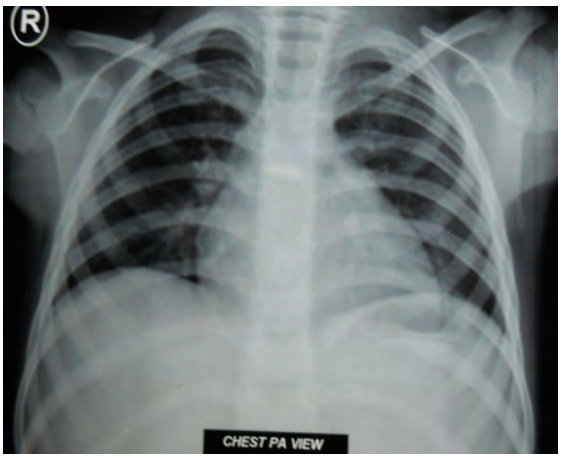
Child received one unit of PRBC transfusion from outside before admission, after all these tests.

After admission, we found Hb-11.4gm/dL; TLC-10,100($N^{48}L^{40}M^{4}E^{8}B^{0}$); Platelet-5,32,000; urea 20, creatinine 0.5, Na-136; K-4.3; total protein 4.1gm/dl (Alb-1.9 and Glb-2.2); Stool for OBT came Positive twice on 28/6 and 29/6.Urine C/S showed a growth of E.coli. Mantoux test was Neg, gastric aspirate (morning sample) on both days came Neg.

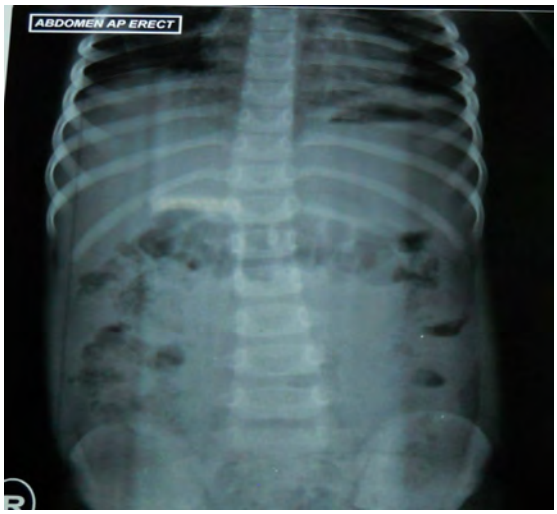
USG whole abdomen detected a gross diffuse colonic wall thickening with minimal ascites. There was also a hepatomegaly with focal hypoechoic lesion in the left lobe. Ascitic fluid was so minimal that it could not be aspirated for study under USG guidance.

2nd Line Investigation:

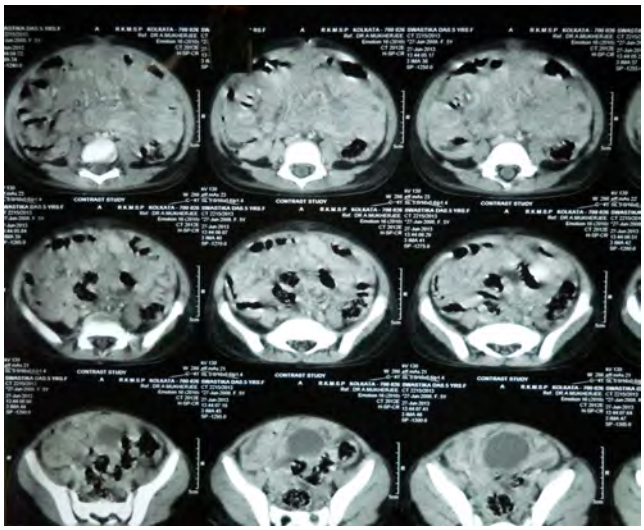
All the primary investigations failed to detect the cause of gutwall thickening. Proper biopsy from gutwall was needed, but there was risk of anesthetia and OT procedure. Finally USG-guided FNAC was taken from bowel-wall. Microscopy showed scattered malignant cells. Those cells had large hyperchromatic nuclei with irregular nuclear membrane and scanty amount of cytoplasm, background showed lymphoglandular bodies.



[Chest X-Ray Shows No Mediastinal Lymphadenopathy.]

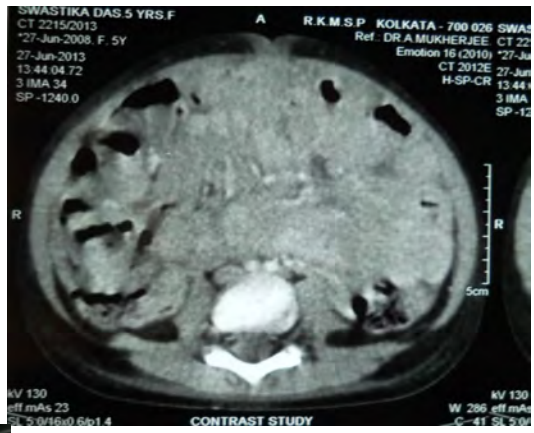


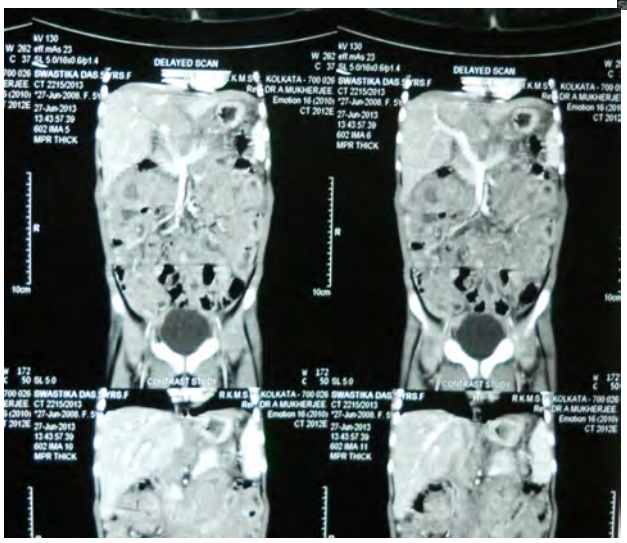
[St. X-Ray Abdomen: Distended Bowel Loops.]



[CECT Abdomen: Diffuse Thickening of The Entire Large Gut, Excluding The Rectum.]

[CECT Abdomen: Abdomen Full of Guts.]





[CECT Abdomen: Abdomen Full of Guts.]

Discussion:

The gastrointestinal tract is the most frequent site of extra-nodal involvement by Non-Hodgkin's lymphoma. Some patients have primary gastrointestinal lymphoma with disease arising from the alimentary tract, but others have generalized lymphoma with associated gastrointestinal involvement. In both forms the stomach is the most commonly involved, followed by the small intestine, pharynx, colon and rarely esophagus.[3]

Exposure to antigens usually occurs at epithelial surfaces of the body including the gastrointestinal tract, respiratory tract, mammary glands and conjunctiva.[4] Lymphoid tissue in these exposed areas is described as mucosa-associated lymphoid tissue(MALT). This tissue can confer local immunologic protection independent of the general immune system.[5] Gut associated lymphoid tissue forms the largest portion of the MALT-system and is the largest immunologic organ in the body(even larger than the Spleen).

The colon is a much less common site of gastrointestinal lymphoma, than is the stomach or small intestine. Primary Non-Hodgkin's lymphoma of the colon usually involves the cecum or the rectum[6]. Patients with this condition can have polypoid, infiltrative or cavitary lesion.[7] The infiltrative form is characterized by a long segment of concentric narrowing with smooth overlying mucosa and thickened irregular haustral folds, caused by infiltration of submucosa by tumor.[7] The differential diagnosis of cavitatory form of lymphoma includes a malignant stromal tumor or a perforated colonic carcinoma.

In contrast, the generalized lymphoma involving the colon is usually manifested by innumerable small, sessile nodules involving long segments of the colon or even the entire colon.[8] This multinodular form of colonic lymphoma can be confused with a familial polyposis syndrome or lymphoid hyperplasia. The disseminated lymphoma of small intestine characteristically involves long segment of bowel,[9] but obstruction is uncommon, because the infiltrating tumor weakens the muscularis propria and does not elicit a desmoplastic response.[9] It can be differentiated from adenocarcinoma by the length of narrowed segment, the degree of narrowing and the absence of significant obstruction.

Gastrointestinal non-Hodgkin lymphomas are usually B-cell in origin,[10] but lymphomas associated with celiac disease may be of T-cell origin.[11] NHL complicating celiac disease involves the proximal jejunam.

A study conducted in Finland, during 1978-88, showed most frequently the disease occurred in middle aged patients,[12] where the stage of the disease was the most important prognostic factor. Five-year survival was 92% in stage-1 disease. The importance of our case is that such an extensive colonic infiltration at 5 yrs of age is a rare presentation.

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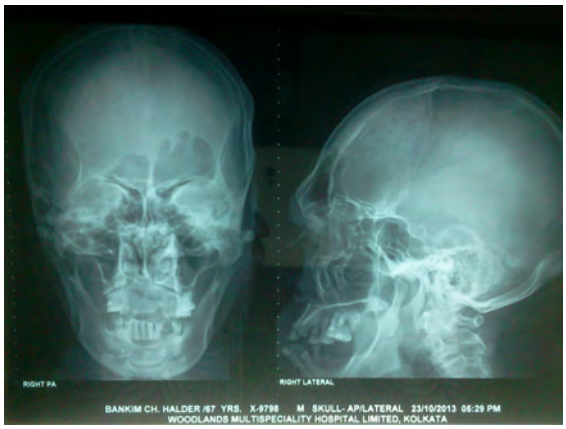
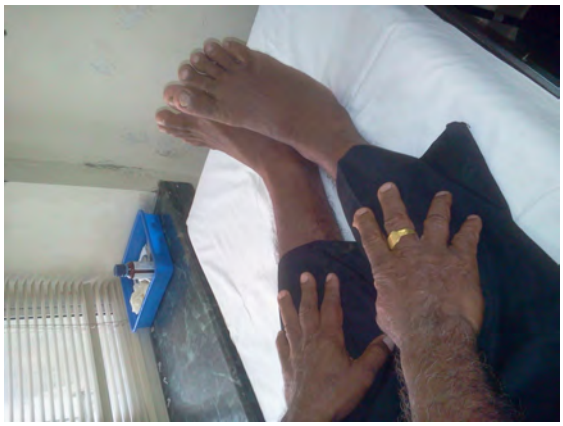
Pictorial CME

Dr. Semanti Chakraborty[1], Prof. Jayanta Chakraborty[2]

WHAT IS THE DIGNOSIS ?





- Answer is Acromegaly.
- The patient came with mild headache and dysuria. X-ray skull reveals hypertrophied paranasal sinuses, frontal bossing and thickened Calvarium.
- Acromegaly is due to anterior pituitary tumor secreting GH or very rarely due to hypothalamic or ectopic secretion of GH/GHRH
- GHRH secretion may occur from bronchial carcinoid, small cell lung cancer, pancreatic islet cell tumor, adrenal adenoma, pheochromocytoma and medullary thyroid carcinoma.
- Some genetic syndromes like Mc Cune Albright syndrome, Carney's syndrome. Familial acromegaly, MEN 1 produces excess GH secretion.
- In > 65% of cases macroadenoma is present, so pressure effects of enlarged pituitary is common. Headache and visual field defects are common….1
- In children tall stature, gigantism as it is called is usual manifestation. Children who are more than three standard deviations (SD) above normal mean height for age, or more than 2 SDs over their adjusted mean parental height.….1
- In adults the dignosis is often delayed until florid facial or acral features are present.
- Patient may attend neurologist for headache, cranial nerve palsy or carpal tunnel syndrome to ophthalmologist for visual field defect, to dental surgeon for dental malocclusion or prognathism.
- May attend rheumatologist for arthritis. Cardiomegaly, diastolic dysfunction, hypertension may draw cardiologist attention.

[1]Senior Resident, [2]Prof. & HOD of Medicine & Endocrinologist, V.I.M.S., RKMSP

Sleep apnea may necessitate pulmonologist referral. A dermatologist may come in the picture for skin tag or hyperhidrosis. Female subjects often consult gynecologist for menstrual disorders or galactorrhoea. We have seen a teacher consulting initially an otorhinolaryngologist for deep and laboured voice. And finally the endocrinologist may diagnose from hyperglycemia, insulin resistance or during evaluation of MEN 1 syndrome.

- **Dignosis** is suspected by GH nadir during an oral OGTT of greater than 1ug/L or 1ng/ml…1. However, Endocrine society guideline recommends consideration of lowering this cutoff to 0.4 ng/mL because of the increased sensitivity of current GH assays…2. Age specific serum IGF-1 level are high and help in diagnosis. False-positive elevations of serum IGF-I levels may be seen in pregnancy, during which the placenta makes large quantities of a smaller yet biologically active GH molecule. IGF-I levels should be compared with age-dependent normative data generated across all age-groups in both sexes..2. Confirmation by pituitary-hypothalamic imaging or very rarely for ectopic secretion by PET, MRI, CT scan…1. Growth hormone-staining of histopathology material and pituitary somatostatin reseptor subtype, in biopsy material help to predict response to somatostatin analogue therapy.

Treatment:

- The goals of therapy for acromegaly are to (*1) control biochemical indices of activity, (2) control tumor size and prevent local mass effects, (3) reduce signs and symptoms of disease, (4) prevent or improve medical comorbidities, and (5) prevent early mortality …2.* The primary mode of therapy is surgery, which is recommended for all patients with microadenomas and for all patients who have macroadenomas with associated mass effects. In patients with macroadenomas without mass effects, and with low likelihood of surgical cure, a role for surgical de-bulking of macroadenomas to improve the response to subsequent medical therapy has been advocated, as well as primary medical therapy alone. Medical therapy is generally used in the adjuvant setting as well as radiotherapy...2.

Somatostatin Analogues (SSA):

The use of SSAs in the management of acromegaly is based principally on the inhibitory effects of native somatostatin on GH secretion. Although the initial formulations for SSAs (octreotide) were administered subcutaneously up to 3 or 4 times a day, the newer formulations are longer acting and Could be used once monthly or longer. Such as Sandostatin LAR and Lanreotide. But short-acting subcutaneously administered octreotide should be given for 2 weeks 3 times daily before initiation of treatment with the long-acting octreotide LAR or Lanreotide in order to assess the response to and systemic tolerability of octreotide. SSAs successfully reduce GH and IGF-I levels in 50% to 70% of patients…2

Sandostatin-LAR is an effective and well-tolerated treatment for patients with acromegaly. Undoubtedly the initial indication for Sandostatin-LAR will be in the patient who is not cured after surgery and radiotherapy, but it may be used as a primary treatment in some acromegalics…3

GH Receptor Antagonist:

Pegvisomant is a recombinantly derived analogue of human GH that acts as a highly selective GH receptor antagonist. Treatment with pegvisomant results in a dose-dependent reduction of serum IGF-I levels but an increase in circulating GH levels. Therefore, serum IGF-I, and not GH, is used to monitor the biochemical response to therapy. Patients receiving this GH receptor antagonist require close observation with serial MRI scans, such as at 6-month intervals during the first year of management and then at annual intervals Pegvisomant therapy is associated with abnormal results of LFTs…2.

Radiation Therapy:

l Pituitary irradiation in acromegaly is generally considered an adjunctive therapy in patients not fully responding to surgical and medical treatments …2.

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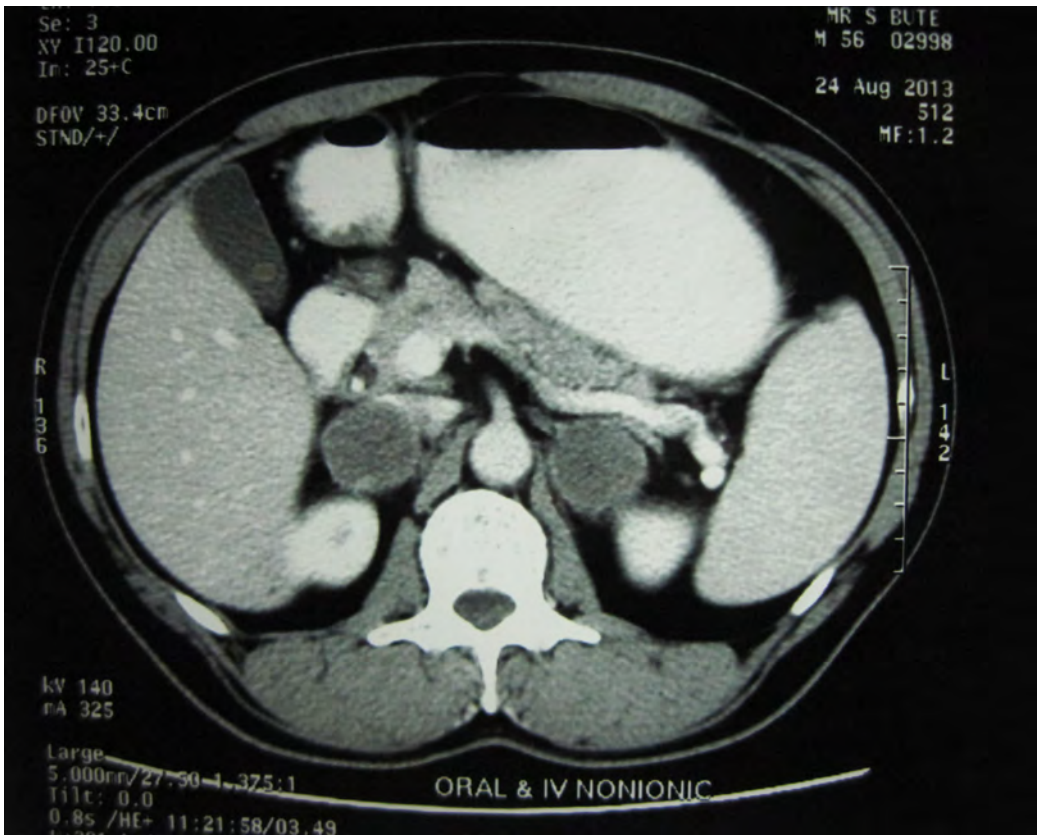
3. J Clin Endocrinol Metab. 1995 Nov; 80 (11) : 3267-72. **Depot long-acting somatostatin analog (Sandostatin-LAR) is an effective treatment for acromegaly.** Stewart PM, Kane K, SE, LancranjanI, Sheppard MC.

Images in Clinical Medicine

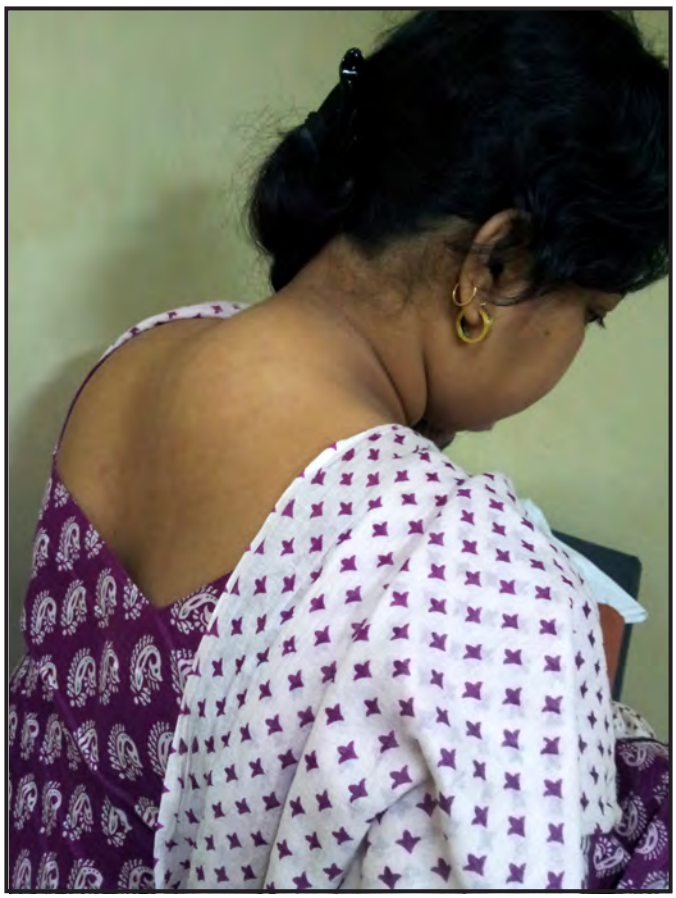
Dr. Sudip Chatterjee



CT scan of a 57 year old male who presented in adrenal crisis. The scan shows bilateral enlarged hypodense adrenals. FNAC found Histoplasmosis. The patient received a course of Itraconazole and is now well on steroid replacement.

Prof., Dept. of Medicine & Endocrinologist, V.I.M.S., RKMSP

Buffalo Hump



Buffalo hump refers to a lump of fat that develops at the top of the back between the shoulders. It can arise from a variety of conditions that are characterized by an increase in central fat distribution. Originally described as clinical feature of Cushings Syndrome, but is now more commonly seen with Obesity. Some consider it to be a clinical sign of insulin resistance. When found in a patient; blood pressure to be measured, other features of Cushings Syndrome to be looked for and blood sugar and basal Cortisol should be measured. The most common cause of Cushings Syndrome in clinical practice is the prolonged use of oral corticosteroid drugs, which are prescribed to treat different conditions, including inflammatory diseases.

Courtesy : Prof. D. Maji (Dept. of Medicine)

Tubercular Laryngitis

Prof. B. K. Roychaudhuri, Dr. A. Roychoudhury, Dr. S. Ghosh

Case report:

32 years old male patient with hoarseness, diagnosed to have tubercular laryngitis and treated with antitubercular drugs.

Pre Therapy Photographs

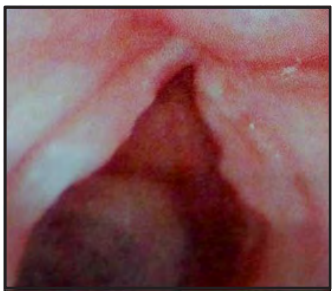


Fig 1: Abducted vocal folds before therapy

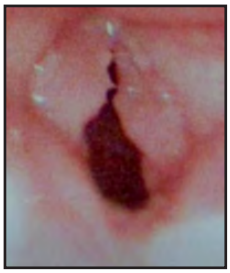


Fig 2: Adducted vocal folds before therapy

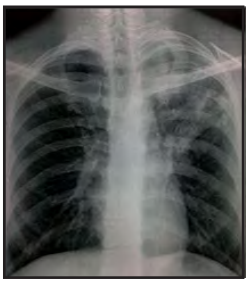


Fig 3: Pre-therapy X-Ray Chest showing patchy opacities involving Left upper lobe

Post Therapy Photographs (after 6 months)

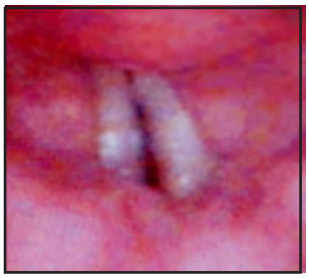


Fig 4: Normal adducted vocal folds

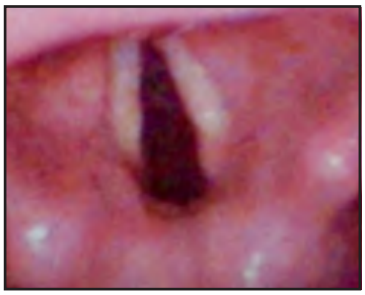


Fig 5: Normal abducted vocal folds

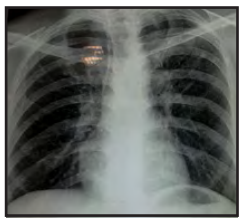


Fig 6 : X-Ray Chest showing normal lung fields with residual fibrosis

Fig. 7: A happy patient after therapy

Dept. of ENT and Head-Neck Surgery, V.I.M.S., RKMSP

Institute News

The 27th Annual Scientific Conference of the institute has been organized successfully by Dr. Himadri Sengupta, Executive President on 26th, 27th & 28th July, 2013. The conference was preceded by a pre-conference workshop on 25th July, 2013.

This year our nursing and paramedical staff organized a joint scientific conference on 26th July, 2013. The whole day seminar was divided in different important sessions. Participants from various institute attended that whole day seminar.

The three day annual scientific conference started from 26th July. The programme included interesting sessions like panel discussion, debate, award paper session, mediquiz etc. Annual Scientific Oration was delivered by Prof. Ambar Chakraborty, Dayananda Oration was given by Prof. P. B. Dutta and Gahananda oration was presented by Prof. Adarsh Chaudhuri, New Delhi.

1. A Video discussion on Cataract Surgery was organized by the Dept. of Opthalmology on 26.08.2013.
2. A CME on the Management of Infertile Couple was organized by South Kolkata Medical Association (Branch of IMA) in collaboration with this Institute on 05.11.2013.
3. A two days' Workshop on Live Phonosurgery & Hands on Cadaver dissection organized by the Department of E.N.T. and Head & Neck surgery was held on 21 & 22 November, 2013, where a good number of participants from this institute and outside attended.

Achievements:

Prof. Arabinda Mukherjee of Neurology department has been elected as "President Elect" of Indian Academy of Neurology, Prof. samar Banerjee of the Department of Medicine has been elected as President of Research Society for study on diabetes in India (RSSDI) and Prof. Ashoke Ganguly department of Dermatology has been awarded FRCP. Prof. Dilip Kr. Mazumdar, Dept. of Medicine has recently been appointed as overseas Regional Advisor for East Region of India in addition to his commitments for West Bengal by the Council of Royal College of Physicians of Edinburgh.

Dr. Sudip Chatterjee published 4 articles in important journals this year & contributed chapters in 2 text books. He also delivered lectures at RIMS Imphal, Endocrine Society conference at Sanfransico, ENICON at Bhopal & presented paper in Medicon International, Kolkata. He was one of the faculty at Ideacon 2013 conference.

We express deep sorrow at the passing away of —

- **DR. SANTOSH KUMAR DUTTA,** *Senior Specialist in Radiodiagnosis on 27th April, 2013.*
- **DR. SHIBANI KAR,** *Consultant in Obs & Gynae on 30th June, 2013.*
- **DR. SUNIL KRISHNA GHOSH,** *Hony. Consultant in Opthalmology on 11th November, 2013.*

We remember with respectful gratitude the dedicated and selfless services rendered by them during their long association with this Institute.

We whole heartedly pray to the Allmighty for the eternal peace of the departed soul.

Editorial Board
Journal of the Vivekananda Institute of Medical Sciences